Data supplement Materials:

1. Data Supplement Material 1: Statistical code
2. Data Supplement Material 2: Flow chart of selection
3. Data Supplement Material 3: Extracted studies
4. Data Supplement Material 4: Summary of extracted data
5. Data Supplement Material 5: Standard random effects meta-analysis for preventative effect against tuberculosis
6. Data Supplement Material 6: Standard random effects meta-analysis for hepatotoxicity
7. Data Supplement Material 7: Study quality
8. Data Supplement Material 8: Posterior distributions of rankings for (a) preventive effect against tuberculosis for each treatment and (b) hepatotoxicity
9. Data Supplement Material 9: Treatment rankings for a) active tuberculosis and b) hepatotoxicity, with 95% credible intervals.
10. Data Supplement Material 10: Standard meta-analysis forest plot for a) active tuberculosis and b) hepatotoxicity
11. Data Supplement Material 11: Odds ratios for hepatotoxicity, derived from the network meta-analysis
12. Data Supplement Material 12: Inconsistency plot for prevention of active tuberculosis
13. Data Supplement Material 13: Funnel plots for publication bias

Data Supplement Material 1: Statistical code

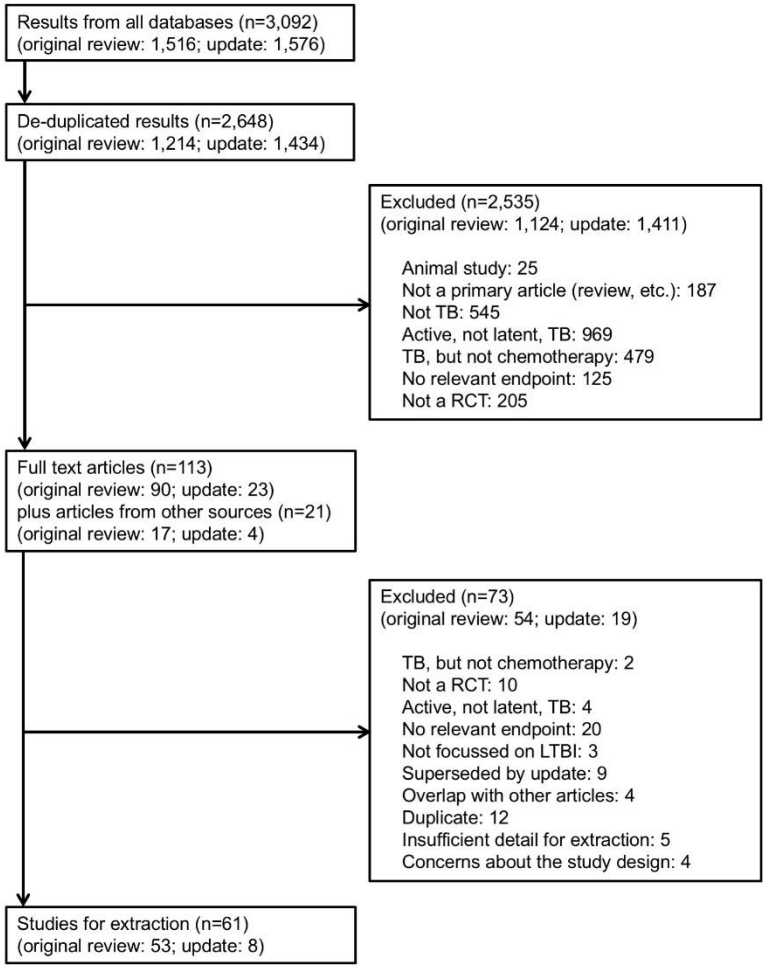
The model is a full random effects model, based on that of Dias *et al*.(15). Adjustment for multi-arm trials is included. As some comparisons involve zero or very low counts, semi-informative priors are used to constrain event rates and odds ratios to sensible bounds where necessary; otherwise both tend towards zero, up to the bounds of the prior. This mainly concerns rifabutin (RFB), which was found to have an unrealistically high and precise estimate of efficacy, despite its sparse data (2 events vs. 0), with unconstrained priors.

```
model{

for(i in 1:NS){
        w[i,1] <-0
        delta[i,t[i,1]]<-0
        mu_prec[i] <- 1/mu_var[i]
        mu[i] ~ dnorm(mu_b, mu_prec[i])  # vague priors for trial baselines
                        ## shouldn't be *too* vague as causes problems with low counts
                        ## specified per-study and only less vague where needed
        for (k in 1:na[i]){
                r[i,k] ~ dbin(p[i,k],n[i,k])   # binomial likelihood
                logit(p[i,k])<-mu[i] + delta[i,t[i,k]]
                rhat[i,k] <- p[i,k] * n[i,k]  # expected value of the numerators
                #Deviance contribution:
                dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
        }
        for (k in 2:na[i]) {
                # trial-specific LOR distributions
                delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
                # mean of LOR distributions
                md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]]  + sw[i,k]
                # precision of LOR distributions
                taud[i,t[i,k]] <- tau *2*(k-1)/k
                # adjustment, multi-arm RCTs
                w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
                # cumulative adjustment for multi-arm trials
                sw[i,k] <-sum(w[i,1:k-1])/(k-1)
        }
        # summed residual deviance contribution for this trial
        resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev<- sum(resdev[]) # Total Residual Deviance

## INH 12m (d[6]) as base
## again, use more informative priors for treatments with
## low data to prevent estimation problems
for (k in 1:5){
        d[k] ~ dnorm(0,dprec[k])
}
d[6]<-0
for (k in 7:NT){
        d[k] ~ dnorm(0,dprec[k])
}

sd~dunif(0,5)                   #  vague prior for random effects standard deviation
tau<-1/pow(sd,2)

}
```

Reference

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Sheffield, United Kingdom: Univ of Sheffield; 2011. Accessed at http://www.nicedsu.org.uk/

Data Supplement Material 2: Flow chart of selection



Data supplement Material 3: Extracted studies

Studies in the update (two update previously included studies)

First author	Journal	Year	Participants	Country of study	Drugs compared	Participants	Hepatotoxicity extractable?	Development of active TB?
Danel(1)	New England Journal of Medicine	2015	HIV type 1 positive individuals, 18 years and older	Ivory coast	No treatment; INH	2056	Yes	Yes
Gray (2)	International Journal of Tuberculosis and Lung Disease	2014	HIV positive children (>8 months) on antiretroviral treatment	South Africa	Placebo; INH	167	No	Yes
Kim (3)	Journal of Antimicrobial Chemotherapy	2015	Kidney transplant recipients, 16 years or older, IGRA positive	Korea	No treatment; INH	263	No	Yes
Ma Lin (4)	National Medical Journal of China	2014	Systemic lupus erythematosus patients, 18 years or older, at high risk of TB	China	No treatment; INH; INH-EMB	203	No	Yes
Rangaka (5)	Lancet	2014	HIV positive individuals, 18 years or older, on ART	South Africa	Placebo; INH	1329	Yes	Yes
Rivero (6)	Enfermedades Infecciosas y Microbiología Clínica	2003	HIV infected anergic patients	Spain	No treatment; INH; RMP+INH; RMP+PZA	319	Yes	Yes
Samandari †(7)	Lancet/ AIDS	2015	HIV positive individuals, 18 years or older	Botswana	INH	1,995	Yes	Yes
Sterling (8)	AIDS	2016	HIV infected individuals, 12 years or older, TST positive or contacts of TB cases	USA, Brazil, Spain, Peru, Canada, Hong Kong	INH; INH-RPT	399	No	Yes

Studies in the previous systematic review

First author	Journal	Year	Participants	Country of study	Drugs compared	Participants	Hepatotoxicity extractable?	Development of active TB?
Agarwal (9)	International Urology and Nephrology	2004	End stage renal disease patients receiving renal transplantation	India	No treatment; INH	85	No	Yes
Bailey (10)	Annals of Internal Medicine	1974	Tuberculin reactive hospital employees	USA	No treatment; INH	178	Yes	No
Bush (11)	American Review of Respiratory Disease	1965	Household contacts	Japan	Placebo; INH	2,238	No	Yes
Chan (12)	International Journal of Tuberculosis and Lung Disease	2012	Male prison inmates with terms more than six months	Taiwan	RMP; INH	373	Yes	No
Comstock (13)	The American Review of Respiratory Disease	1967	Individuals over two months of age	USA	Placebo; INH	6,064	No	Yes
Cowie (14)	Tubercle and Lung Disease	1996	Gold miners with chronic silicosis	South Africa	Placebo; INH-RMP-PZA	382	No	Yes
Debre (15)	International Journal of Epidemiology	1973	Young people with recent tuberculin conversion	France	No treatment; INH	2,970	No	Yes
Del Castillo (16)	Bull Quezon Institute	1965	Household contacts	Philippines	Placebo; INH	293	No	Yes
Egsmose (17)	Bulletin of the World Health Organization	1965	Household contacts of pulmonary TB cases	Kenya	Placebo; INH	775	No	Yes
Falk (18)	Chest	1978	Outpatient clinics for veterans diagnosed with inactive pulmonary TB	USA	Placebo; INH	7,036	No	Yes

Ferebee (19)	American Review of Respiratory Disease	1962	Household contacts of active TB cases	USA	Placebo; INH	6,219 households	No	Yes
Ferebee (20)	American Review of Respiratory Disease	1963	Patients in mental hospitals	USA	Placebo; INH	25,210	No	Yes
Fitzgerald (21)	Journal of Acquired Immune Deficiency Syndromes	2001	HIV positive individuals, but symptom free, individuals	Haiti	No treatment; INH	237	No	Yes
Geijo (22)	Enfermedades Infecciosas y Microbiología Clínica	2007	Individuals meeting the 1990 CDC recommendations	Spain	INH; INH-RMP	96	Yes	Yes
Gordin (23)	The New England Journal of Medicine	1997	HIV positive individuals, over 13 years old	USA	Placebo; INH	517	Yes	Yes
Gordin†(24,25)	Journal of the American Medical Association/Clinical Infectious Diseases	2000/ 2004	HIV positive individuals	USA, Mexico, Haiti, Brazil	INH; RMP-PZA	1,583	Yes	Yes
Gupta (26)	Journal of Tuberculosis	1993	Children of TB patients	India	No treatment; INH; INH-RMP; INH-RMP-PZA	415	No	Yes
Halsey (27)	Lancet	1998	HIV positive adults from outpatient clinics and general community	Haiti	INH; RMP-PZA	750	No	Yes
Hawken (28)	AIDS	1997	HIV positive individuals, 14-65 years of age	Kenya	Placebo; INH	684	No	Yes
Hong Kong Chest Service/TB Research Centre, Madras/ British Medical Research Council (29)	The American Review of Respiratory Disease	1992	Silicosis patients under 65	Hong Kong	Placebo; INH; INH-RMP; RMP	679	No	Yes

Horwitz (30)	Bulletin of the World Health Organization	1966	Over 15 years of age. Regimen allocated by village	Greenland	INH; INH 'at placebo levels'	8,081	Yes	Yes
International Union Against Tuberculosis Committee on Prophylaxis (31)	Bulletin of the World Health Organization	1982	Mostly individuals 20-64 years of age	Czechoslovakia, Finland, German Democratic Republic, Hungary, Poland, Romania, Yugoslavia	Placebo; INH	27,830	No	Yes
Jimenez-Fuentes (32)	The International Journal of Tuberculosis and Lung Disease	2013	Immigrants (within last 5 years) from high-burden countries	Spain	INH; INH-RMP	590	Yes	Yes
John (33)	Transplantation	1994	Haemodialysis patients	India	Placebo; INH	184	Yes	Yes
Leung (34)	Chest	2003	Silicosis patients	Hong Kong	INH; RMP-PZA	76	Yes	No
Madhi (35)	The New England Journal of Medicine	2011	Infants between 91-120 days of life	South Africa, Botswana	Placebo; INH	1,351	Yes	Yes
Magdorf (36)	Pneumologie	1994	Children, recent TST conversion	Germany	INH; RMP; RMP-PZA	150	No	Yes
Martinez Alfaro (37)	Medicina Clinica	1998	Inclusion criteria: 1990 CDC guidelines	Spain	INH; INH-RMP	196	Yes	Yes
Martinez Alfaro (38)	Medicina Clinica	2000	HIV positive individuals, 1990 CDC and ATS recommendations	Spain	INH; INH-RMP	133	Yes	Yes
Martinson (39)	The New England Journal of Medicine	2011	HIV positive individuals, over 18 years old	South Africa	INH; INH-RMP; INH-RPT	1,148	Yes	Yes
Matteelli (40)	The International Journal of Tuberculosis and Lung Disease	1999	HIV positive individuals, over 18 years old	Italy	INH; INH-RFB	44	No	Yes

Menzies (41)	American Journal of Respiratory and Critical Care Medicine	2004	Respiratory hospital patients, over 18 years old	Canada	INH; RMP	116	Yes	No
Menzies (42)	Annals of Internal Medicine	2008	Hospital patients over 18 years of age	Canada, Saudi Arabia, Brazil	INH; RMP	840	Yes	No
Mohammed (43)	The International Journal of Tuberculosis and Lung Disease	2007	HIV positive individuals (WHO clinical stage three or four), over 18 years of age	South Africa	Placebo; INH	98	Yes	Yes
Mount (44)	American Review of Respiratory Disease	1962	Household contacts of active TB cases	USA	Placebo; INH	2,814	No	Yes
Naqvi (45)	Nephrology, dialysis, transplantation	2010	Renal transplant recipients	Pakistan	No treatment; INH	402	No	Yes
Pape (46)	Lancet	1993	Individuals newly diagnosed with HIV, 18-65 years old	Haiti	No treatment; INH	118	No	Yes
Portilla (47)	Enfermedades Infecciosas y Microbiología Clínica	2003	HIV negative intravenous drugs users	Spain	INH	37	No	Yes
Quigley (48)	AIDS	2001	HIV positive individuals, over 15 year olds	Zambia	Placebo; INH; RMP-PZA	1,053	No	Yes
Rivero (49)	Enfermedades Infecciosas y Microbiología Clínica	2007	HIV positive individuals	Spain	INH; INH-RMP; RMP-PZA	308	Yes	Yes
Sanchez-Arcilla (50)	Medicina Clinica	2004	Homeless individuals	Spain	INH; RMP-PZA	172	Yes	No

Samandari †(7,51)	Lancet/ AIDS	2011/ 2015	HIV positive individuals, 18 years or older	Botswana	INH	1,995	Yes	Yes
Schechter (52)	American Journal of Respiratory and Critical Care Medicine	2006	Household contacts	Brazil	INH-RPT; RMP	399	Yes	Yes
Spyridis (53)	Clinical Infectious Diseases	2007	Children under 15 years old in a TB clinic without active TB	Greece	INH; INH-RMP	926	No	Yes
Sterling (54)	The New England Journal of Medicine	2011	Close contacts	USA, Canada, Brazil, Spain	INH; INH-RPT	7,731	Yes	Yes
Swaminathan (55)	PLoS ONE	2012	HIV positive adults	India	INH (plus some with CTX); INH-EMB (plus some with CTX)	712	No	Yes
Tortajada (56)	The International Journal of Tuberculosis and Lung Disease	2005	Contacts with recent TST conversion, under 35 years old	Spain	INH; RMP-PZA	352	Yes	No
Veening (57)	Bulletin of the International Union of Tuberculosis	1968	Recruits in marine camp of Royal Navy exposed to an infectious TB case	Netherlands	Placebo; INH	261	No	Yes
Vikrant (58)	Transplant infectious disease	2005	Renal transplant recipients, over 14 years of age	India	No treatment; INH	109	Yes	Yes
Whalen/Johnson† (59,60)	The New England Journal of Medicine/AIDS	1997/ 2001	HIV positive, 18-50 year old males and non-pregnant females	Uganda	Placebo; INH; INH-RMP; INH-RMP-PZA	2,736	Yes	Yes
White (61)	Journal of Correctional Health Care	2012	Prison inmates diagnosed with LTBI at entry	USA	INH; RMP	364	Yes	No

Xie (62)	Journal of Sichuan University	2009	Chinese patients with rheumatoid arthritis receiving long-term methotrexate therapy	China	MTX; INH-MTX	201	No	Yes
Zar (63)	British Medical Journal	2007	HIV positive children	South Africa	Placebo-CTX; INH-CTX	263	No	Yes

† For these two entries a single study is represented, but there were two publications. In each case one presented the most up-to-date results for the number of active TB cases (Gordin 2000/Johnson/Samandari 2015) and the other AEs (Gordin 2004/Whalen/Samandari 2011).

ATS- American Thoracic Society; CDC- Centres for Disease Control and Prevention, USA; CTX- co-trimoxazole; EMB- ethambutol; IGRA- interferon-γ release assay; INH- isoniazid; MTX- methotrexate; PPD-purified protein derivative; PZA- pyrazinamide; RFB- rifabutin; RMP- rifampicin; RPT- rifapentine; TST- tuberculin skin test; TB- tuberculosis; WHO- World Health Organization

Data Supplement Material 4: Summary of extracted data

Summary of extracted data across every study included in the analysis, presented by treatment regimen (rows).Columns count the number of a) studies and b) participants for whom data are available for each row, subdivided as to whether data were presented for hepatotoxicity or the development of active TB.

	Studies			Participants		
Description	**All**	**TB**	**Hepa - toxicity**	**All**	**TB**	**Hepa - toxicity**
No treatment	12	11	5	3,363	170	19
Placebo	28	27	6	48,308	1,206	66
INH 3-4m	4	3	0	7,231	87	0
INH 6m	25	20	14	18,084	533	83
INH 9m	8	5	6	6,350	31	144
INH 12m	29	27	10	46,271	448	142
RFB-INH	1	1	0	16	0	0
RFB-INH (high)	1	1	0	14	0	0
RPT-INH	4	4	4	4,726	36	39
RMP	6	2	4	1,068	20	4
RMP-INH 1m	1	1	0	83	9	0
RMP-INH 3-4m	10	10	8	1,833	88	36
RMP-INH-PZA	3	3	1	733	26	1
RMP-PZA	10	7	7	2,220	75	79
INH-EMB	1	1	0	357	22	0
INH-EMB 12m	1	1	0	66	0	0
Total	144	124	65	140,723	2,751	613

EMB- ethambutol; INH- isoniazid; PZA- pyrazinamide; RFB- rifabutin; RMP- rifampicin; RPT- rifapentine; TB- tuberculosis

Data Supplement Material 5: Standard random effects meta-analysis for preventative effect against tuberculosis*

a)

Baseline	Comparator	N	OR (95% CI)	I^2 (p-value)	Publication bias†
No treatment	INH 3-4m	1	0.56 (0.24-1.30)		
No treatment	INH 6m	3	0.47 (0.30-0.73)	0.0% (p=0.482)	
No treatment	INH 9m	2	0.37 (0.18-0.76)	0.0% (p=0.508)	
No treatment	INH 12m	5	0.40 (0.19-0.84)	40.3% (p=0.153)	0.300
No treatment	RMP-INH 1m	1	0.49 (0.20-1.16)		
No treatment	RMP-INH 3-4m	2	0.33 (0.10-1.12)	40.3% (p=0.196)	
No treatment	RMP-INH-PZA	1	0.02 (0.00-0.41)		
No treatment	RMP-PZA	1	0.24 (0.03-2.20)		
Placebo	INH 3-4m	2	0.30 (0.03-3.03)	80.6% (p=0.023)	
Placebo	INH 6m	9	0.61 (0.48-0.77)	46.5% (p=0.060)	0.654
Placebo	INH 12m	17	0.53 (0.42-0.67)	57.7% (p=0.002)	0.348
Placebo	RMP	1	0.48 (0.26-0.87)		
Placebo	RMP-INH 3-4m	2	0.52 (0.33-0.84)	33.8% (p=0.219)	
Placebo	RMP-INH-PZA	2	0.47 (0.22-0.98)	53.7% (p=0.141)	
Placebo	RMP-PZA	1	0.80 (0.49-1.31)		
Placebo	INH-EMB 12m	1	0.06 (0.00-0.98)		
INH 3-4m	INH 6m	1	0.44 (0.30-0.67)		
INH 3-4m	INH 12m	1	0.32 (0.20-0.50)		
INH 3-4m	RMP-INH 1m	1	0.88 (0.34-2.28)		
INH 3-4m	RMP-INH 3-4m	1	0.36 (0.11-1.18)		
INH 3-4m	RMP-INH-PZA	1	0.04 (0.00-0.74)		
INH 6m	INH 12m	3	0.69 (0.51-0.93)	0.0% (p=0.977)	
INH 6m	RFB-INH	1	0.15 (0.01-3.45)		
INH 6m	RFB-INH (high)	1	0.17 (0.01-3.94)		
INH 6m	RPT-INH	1	1.09 (0.60-1.99)		
INH 6m	RMP	1	0.78 (0.41-1.46)		
INH 6m	RMP-INH 3-4m	7	0.90 (0.65-1.23)	0.0% (p=0.729)	0.876
INH 6m	RMP-INH-PZA	1	0.50 (0.27-0.92)		
INH 6m	RMP-PZA	5	1.03 (0.67-1.59)	0.0% (p=0.717)	0.730
INH 9m	RPT-INH	1	0.44 (0.18-1.07)		
INH 9m	RMP-INH 3-4m	1	3.03 (0.12-75.32)		
INH 12m	RPT-INH	1	1.54 (0.68-3.51)		
INH 12m	RMP-INH 3-4m	2	1.06 (0.35-3.21)	36.9% (p=0.208)	
INH 12m	RMP-PZA	1	0.97 (0.57-1.64)		
INH 12m	INH-EMB	1	1.73 (0.86-3.49)		

Baseline	Comparator	N	OR (95% CI)	I^2 (p-value)	Publication bias†
RPT-INH	RMP-INH 3-4m	1	1.00 (0.55-1.79)		
RPT-INH	RMP-PZA	1	0.35 (0.04-3.42)		
RMP	RMP-INH 3-4m	1	1.40 (0.75-2.62)		
RMP	RMP-PZA	1	3.06 (0.12-76.95)		
RMP-INH 1m	RMP-INH 3-4m	1	0.41 (0.12-1.37)		
RMP-INH 1m	RMP-INH-PZA	1	0.05 (0.00-0.85)		
RMP-INH 3-4m	RMP-INH-PZA	2	0.51 (0.10-2.72)	41.5% (p=0.191)	
RMP-INH 3-4m	RMP-PZA	2	0.37 (0.10-1.42)	0.0% (p=0.943)	

* Results of standard random effects meta-analysis (or single study estimates) for all comparisons of regimens for the preventative effect against tuberculosis. Where N>1, heterogeneity is assessed via the I^2 statistic (with p-value); where N>4 publication bias is assessed via the Harbord test. †- p-value from Harbord test, 95% CI- 95% confidence interval, EMB- ethambutol, INH- isoniazid, N- number of comparisons, OR- odds ratio, PZA- pyrazinamide, RFB- rifabutin, RMP- rifampicin, RPT- rifapentine

Data Supplement Material 6: Standard random effects meta-analysis for hepatotoxicity*

Outcome	Baseline	Comparator	N	OR (95% CI)	I^2 (p-value)	Publication bias†
AE	No treatment	INH 6m	2	0.92 (0.42-2.02)	0.0% (p=0.873)	
AE	No treatment	INH 12m	2	4.96 (0.27-90.38)	73.3% (p=0.053)	
AE	Placebo	INH 6m	1	0.99 (0.42-2.32)		
AE	Placebo	INH 12m	4	0.87 (0.40-1.92)	57.9% (p=0.068)	
AE	Placebo	RMP-INH-PZA	1	3.02 (0.12-74.32)		
AE	INH 6m	INH 12m	2	2.92 (0.90-9.44)	74.1% (p=0.049)	
AE	INH 6m	RPT-INH	1	1.00 (0.50-1.99)		
AE	INH 6m	RMP	1	0.03 (0.00-0.48)		
AE	INH 6m	RMP-INH 3-4m	5	0.83 (0.49-1.42)	0.0% (p=0.783)	0.160
AE	INH 6m	RMP-INH-PZA	1	3.49 (0.14-85.82)		
AE	INH 6m	RMP-PZA	5	2.78 (1.25-6.16)	39.3% (p=0.159)	0.757
AE	INH 9m	RPT-INH	1	0.16 (0.10-0.27)		
AE	INH 9m	RMP	3	0.17 (0.06-0.47)	0.0% (p=0.982)	
AE	INH 9m	RMP-INH 3-4m	1	0.73 (0.24-2.20)		
AE	INH 12m	RPT-INH	1	0.20 (0.11-0.37)		
AE	INH 12m	RMP-INH 3-4m	2	0.20 (0.11-0.35)	0.0% (p=0.452)	
AE	INH 12m	RMP-PZA	1	1.26 (0.58-2.70)		
AE	RPT-INH	RMP-INH 3-4m	1	0.87 (0.43-1.78)		
AE	RPT-INH	RMP-PZA	1	7.98 (1.79-35.58)		
AE	RMP-INH 3-4m	RMP-INH-PZA	1	3.62 (0.15-89.02)		
AE	RMP-INH 3-4m	RMP-PZA	2	2.08 (0.85-5.07)	0.0% (p=0.461)	

* Results of standard random effects meta-analysis (or single study estimates) for all comparisons of regimens for hepatotoxicity. Where N>1, heterogeneity is assessed via the I^2 statistic (with p-value); where N>4 publication bias is assessed via the Harbord test. †- p-value from Harbord test, 95% CI- 95% confidence interval, EMB- ethambutol, INH- isoniazid, N- number of comparisons, OR- odds ratio, PZA- pyrazinamide, RFB- rifabutin, RMP- rifampicin, RPT- rifapentine

Data Supplement Material 7: Study quality

Studies in the update

Author	Year	Selection bias: Random sequence generation	Selection bias: Allocation concealment	Performance bias: Blinding of participants and personnel	Detection bias: Blinding of outcome assessment	Attrition bias: Incomplete outcome data	Reporting bias: Selective reporting
Danel	2015	+	?	-	-	+	?
Gray	2014	+	+	+	+	-	?
Kim	2015	+	+	-	-	-	?
Ma Lin	2014	+	?	-	-	?	-
Rangaka	2014	+	+	+	+	+	?
Rivero	2003	+	-	-	-	+	?
Samandari	2015	+	+	+	+	+	?
Sterling	2016	+	-	-	+	+	?

Studies in the previous systematic review

Author	Year	Selection bias: Random sequence generation	Selection bias: Allocation concealment	Performance bias: Blinding of participants and personnel	Detection bias: Blinding of outcome assessment	Attrition bias: Incomplete outcome data	Reporting bias: Selective reporting
Agarwal	2004	?	?	-	-	+	-
Bailey	1974	?	?	?	?	?	+
Bush	1965	?	?	+	?	+	+
Chan	2012	+	?	-	+	+	+
Comstock	1967	+	?	+	+	+	+
Cowie	1996	?	?	?	+	+	+
Debre	1973	+	-	-	?	-	+

Del Castillo	1965	?	?	+	?	+	+
Egsmose	1965	+	?	+	+	+	+
Falk	1978	+	+	+	+	-	+
Ferebee	1962	?	?	+	?	+	+
Ferebee	1963	?	?	?	?	-	+
Fitzgerald	2001	?	?	?	+	+	+
Geijo	2007	+	+	-	-	+	+
Gordin	1997	+	?	+	+	+	+
Gordin	2000/ 2004	?	?	?	?	?	+
Gupta	1993	?	?	?	?	?	+
Halsey	1998	+	+	?	?	+	+
Hawken	1997	+	+	?	?	-	+
Hong Kong Chest Service/ TB Research Centre, Madras/ British Medical Research Council	1992	?	+	+	+	+	+
Horwitz	1966	+	?	?	?	?	+
International Union Against Tuberculosis Committee on Prophylaxis	1982	?	+	?	?	+	+
Jimenez-Fuentes	2013	?	?	?	?	-	+
John	1994	+	?	+	?	-	-
Leung	2003	+	?	?	?	-	+
Madhi	2011	?	?	+	?	-	+
Magdorf	1994	?	?	?	?	+	+
Martinez Alfaro	1998	+	?	-	-	-	+
Martinez Alfaro	2000	?	?	-	-	+	+
Martinson	2011	+	+	-	-	?	?
Matteelli	1999	?	?	-	-	?	+
Menzies	2004	+	+	-	-	+	+

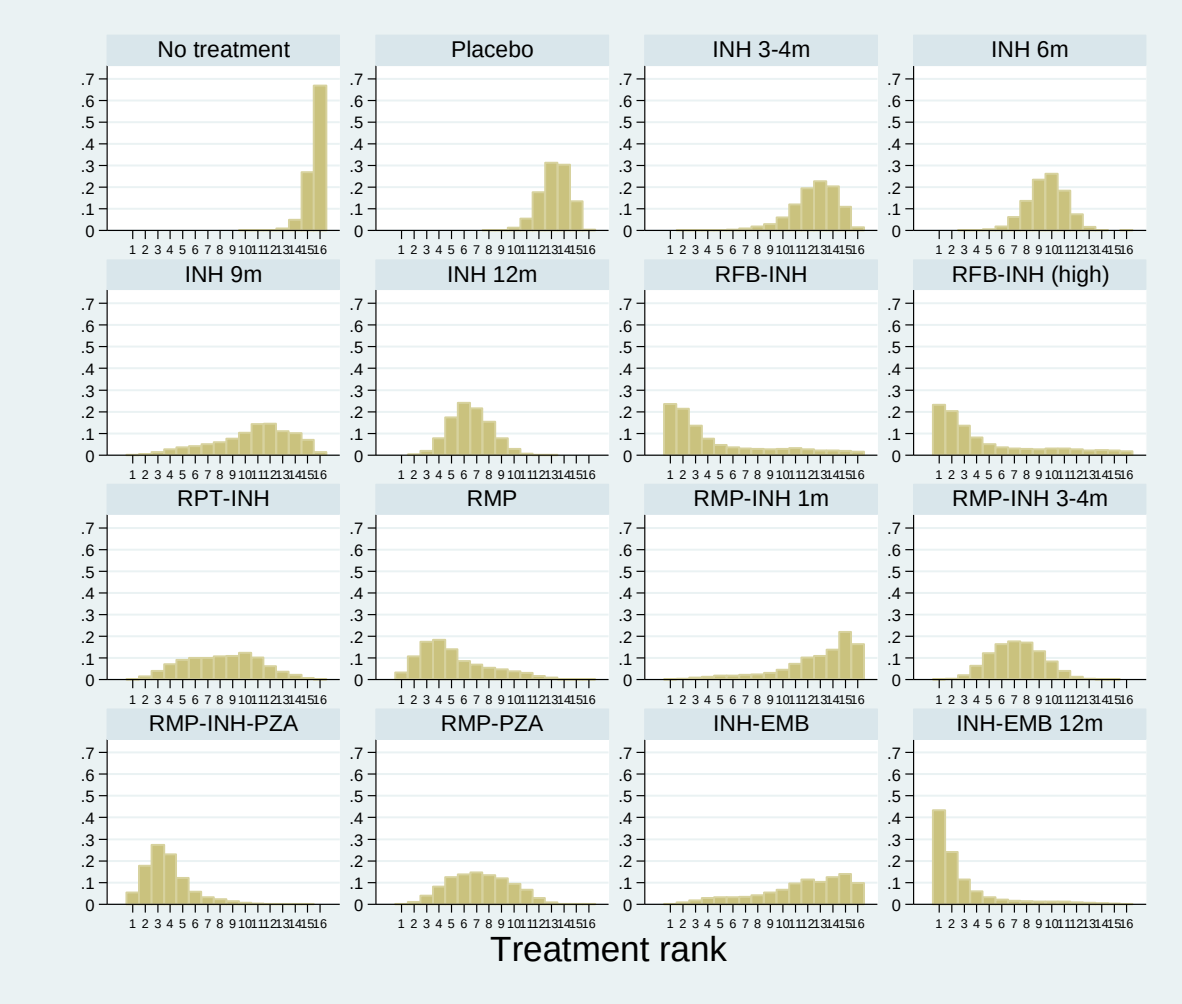
Menzies	2008	+	+	-	-	+	+
Mohammed	2007	+	+	+	+	+	?
Mount	1962	?	?	+	?	+	+
Naqvi	2010	+	?	?	?	?	?
Pape	1993	?	?	?	?	?	+
Portilla	2003	?	?	-	?	+	?
Quigley	2001	+	+	+	?	-	+
Rivero	2007	?	?	?	-	+	+
Samandari	2011	+	+	+	+	+	+
Sanchez-Arcilla	2004	?	?	-	?	-	?
Schechter	2006	+	+	?	?	+	+
Spyridis	2007	+	+	?	?	?	+
Sterling	2011	?	?	-	-	?	+
Swaminathan	2012	+	+	-	+	-	+
Tortajada	2005	?	+	-	-	-	+
Veening	1968	?	?	+	?	+	+
Vikrant	2005	?	?	?	?	+	+
Whalen/Johnson	2001/ 1997	?	+	+	+	-	+
White	2012	?	?	-	?	-	+
Xie	2009	-	-	?	+	+	+
Zar	2007	?	?	+	?	+	+

Utilising the quality assessment tool of Higgins *et al.* (64)

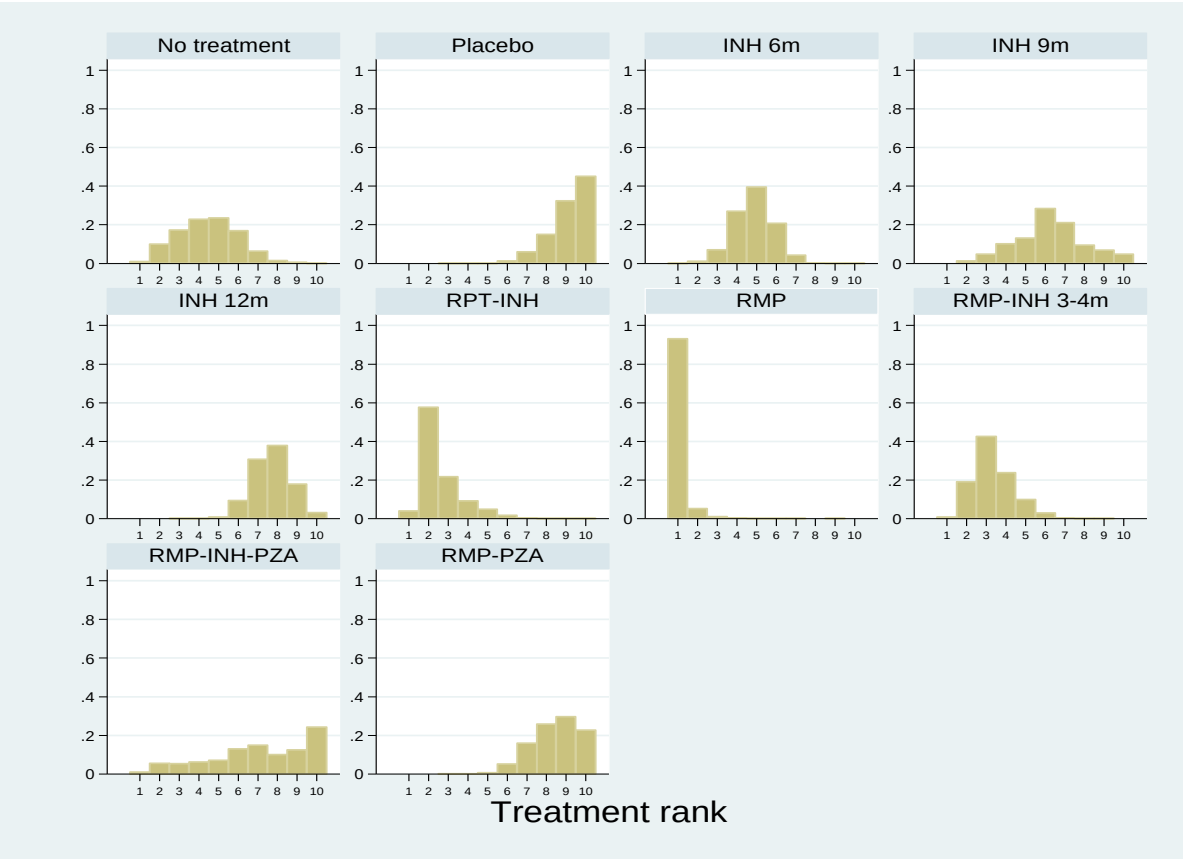
+Low Risk -High Risk ?Unclear Risk

Data Supplement Material 8: Posterior distributions of rankings for (a) preventive effect against tuberculosis for each treatment and (b) hepatotoxicity*

(a)



(b)



* a) Prevention of development of active tuberculosis, b) hepatotoxicity. Posterior distributions of parameters reflect the statistical uncertainty of quantities of interest. In this case, the height of the bars in the histogram reflects the probability of it being the true rank for that treatment. For instance, no treatment has a high probability (over 70%) of having the worst rank for the prevention of active tuberculosis in panel a). 3-4m- 3-4 months, etc., EMB- ethambutol, INH- isoniazid, PZA- pyrazinamide, RFB- rifabutin, RMP- rifampicin, RPT- rifapentine

Data Supplement Material 9: Treatment rankings for a) active tuberculosis and b) hepatotoxicity, with 95% credible intervals. Numbers of comparisons within strata are shown within parentheses (maximum 16).*

a)

		Within-country incidence		Immuno-compromised?		HIV-positive individuals?		
Regimen	**All data (16)**	**Low (12)**	**High (14)**	**No (12)**	**Yes (13)**	**Strictly no* (9)**	**Strictly/ Probably no* (13)**	**Yes (12)**
No treatment	16 (14-16)	11 (5-12)	14 (12-14)	11 (7-12)	13 (11-13)	9 (3-9)	13 (11-13)	11 (9-12)
Placebo	13 (11-15)	12 (9-12)	11 (9-13)	9 (6-11)	11 (9-12)	8 (5-9)	11 (8-12)	9 (7-11)
INH 3-4m	13 (8-15)	10 (4-12)	13 (6-14)	8 (4-11)		6 (2-9)	10 (5-12)	
INH 6m	10 (7-12)	8 (4-11)	8 (5-10)	6 (3-10)	8 (6-10)	5 (2-8)	7 (3-10)	7 (4-9)
INH 9m	12 (5-15)	6 (2-11)	2 (1-12)	8 (1-12)	11 (5-13)	6 (2-9)	9 (3-12)	12 (4-12)
INH 12m	6 (4-10)	6 (3-9)	5 (3-8)	4 (2-8)	6 (3-8)	4 (1-7)	6 (3-9)	5 (3-8)
RFB-INH	3 (1-15)	3 (1-11)	9 (4-13)		3 (1-12)			2 (1-11)
RFB-INH (high)	3 (1-15)	4 (1-11)			3 (1-12)			2 (1-11)
RPT-INH	7 (3-13)	2 (1-9)		10 (1-12)	6 (2-10)	4 (1-8)	5 (1-12)	7 (2-10)
RMP	5 (1-12)	3 (1-11)	4 (1-10)	3 (1-9)			4 (1-10)	
RMP-INH 1m	14 (5-16)		12 (5-14)	9 (3-12)			11 (4-13)	
RMP-INH 3-4m	7 (4-11)	5 (2-10)	6 (3-9)	4 (1-9)	6 (3-10)	2 (1-7)	5 (2-10)	5 (2-8)
RMP-INH-PZA	4 (1-8)	5 (2-9)	3 (1-6)	2 (1-7)	3 (1-8)		3 (1-9)	2 (1-6)
RMP-PZA	7 (3-12)		8 (3-12)	4 (1-11)	7 (3-10)	2 (1-7)	3 (1-11)	5 (2-9)
INH-EMB	12 (3-16)		10 (3-14)		11 (4-13)			10 (3-12)
INH-EMB 12m	2 (1-11)		1 (1-9)		2 (1-9)		2 (1-10)	

b)

Regimen	All data (16)	Within-country incidence		Immuno-compromised?		HIV-positive individuals?		
		Low (12)	High (14)	No (12)	Yes (13)	Strictly no* (9)	Strictly/ Probably no* (13)	Yes (12)
No treatment	16 (14-16)	11 (5-12)	14 (12-14)	11 (7-12)	13 (11-13)	9 (3-9)	13 (11-13)	11 (9-12)
Placebo	13 (11-15)	12 (9-12)	11 (9-13)	9 (6-11)	11 (9-12)	8 (5-9)	11 (8-12)	9 (7-11)
INH 3-4m	13 (8-15)	10 (4-12)	13 (6-14)	8 (4-11)		6 (2-9)	10 (5-12)	
INH 6m	10 (7-12)	8 (4-11)	8 (5-10)	6 (3-10)	8 (6-10)	5 (2-8)	7 (3-10)	7 (4-9)
INH 9m	12 (5-15)	6 (2-11)	2 (1-12)	8 (1-12)	11 (5-13)	6 (2-9)	9 (3-12)	12 (4-12)
INH 12m	6 (4-10)	6 (3-9)	5 (3-8)	4 (2-8)	6 (3-8)	4 (1-7)	6 (3-9)	5 (3-8)
RFB-INH	3 (1-15)	3 (1-11)	9 (4-13)		3 (1-12)			2 (1-11)
RFB-INH (high)	3 (1-15)	4 (1-11)			3 (1-12)			2 (1-11)
RPT-INH	7 (3-13)	2 (1-9)		10 (1-12)	6 (2-10)	4 (1-8)	5 (1-12)	7 (2-10)
RMP	5 (1-12)	3 (1-11)	4 (1-10)	3 (1-9)			4 (1-10)	
RMP-INH 1m	14 (5-16)		12 (5-14)	9 (3-12)			11 (4-13)	
RMP-INH 3-4m	7 (4-11)	5 (2-10)	6 (3-9)	4 (1-9)	6 (3-10)	2 (1-7)	5 (2-10)	5 (2-8)
RMP-INH-PZA	4 (1-8)	5 (2-9)	3 (1-6)	2 (1-7)	3 (1-8)		3 (1-9)	2 (1-6)
RMP-PZA	7 (3-12)		8 (3-12)	4 (1-11)	7 (3-10)	2 (1-7)	3 (1-11)	5 (2-9)
INH-EMB	12 (3-16)		10 (3-14)		11 (4-13)			10 (3-12)
INH-EMB 12m	2 (1-11)		1 (1-9)		2 (1-9)		2 (1-10)	

* Results are shown for a) preventative effect against tuberculosis and b) hepatotoxicity across all data and stratified by country incidence of tuberculosis, immunosuppression and whether the study was on HIV positive individuals, the latter defined as *strictly no* (explicitly stating no or <5% HIV in participants), *strictly or probably no* (which also includes studies that do not mention HIV and any studies prior to 1990) and *yes*, where all participants had HIV. Where subgroups do not contain some treatments, rankings are within a narrower range. EMB- ethambutol, INH-

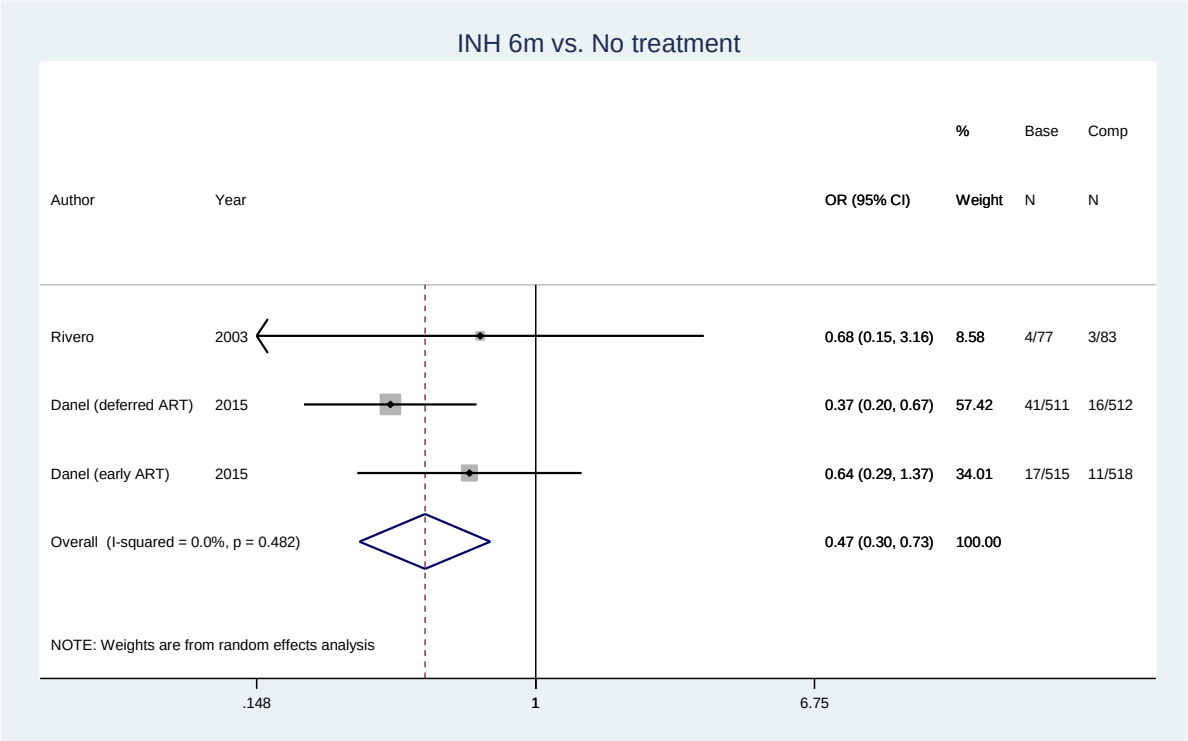
isoniazid, PZA- pyrazinamide, RFB- rifabutin, RFP-INH (high)- a higher dose of RFB, RMP- rifampicin, RPT- rifapentine, TB- tuberculosis

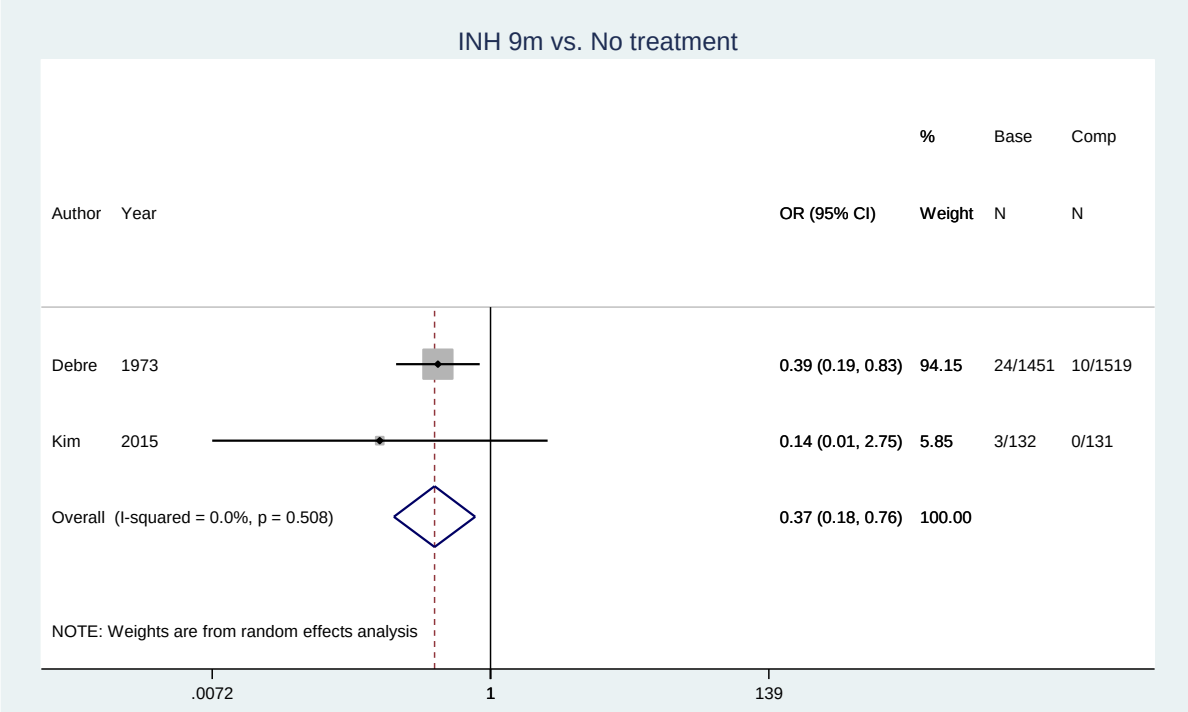
c) Stratified study numbers:

		Studies			Participants		
Strata		**All**	**TB**	**Hepa-toxicity**	**All**	**TB**	**Hepa-toxicity**
Within-country incidence	Low	25	18	15	102410	721	307
	High	37	34	13	37914	2022	296
Immuno-compromised?	No	29	20	12	112158	1668	129
	Yes	33	32	16	28166	1075	474
HIV-positive individuals?	Strictly/probably no	37	28	15	113801	1776	223
	Yes	25	24	13	19191	953	269

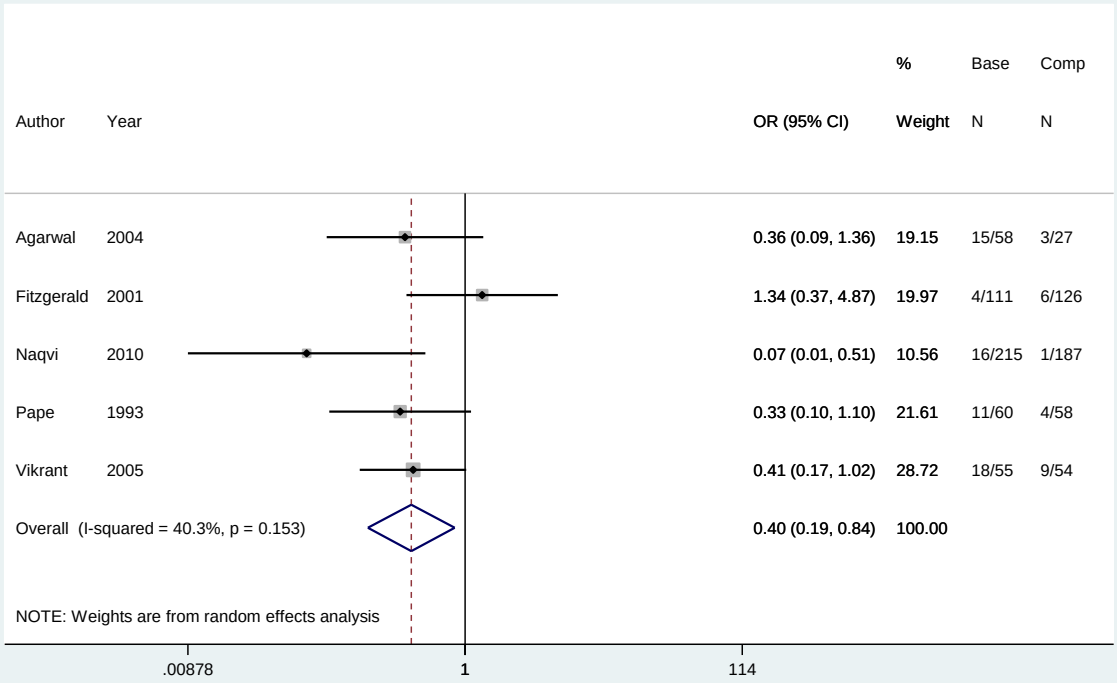
Data Supplement Material 10: Standard meta-analysis forest plot for a) active tuberculosis and b) hepatotoxicity

(a)

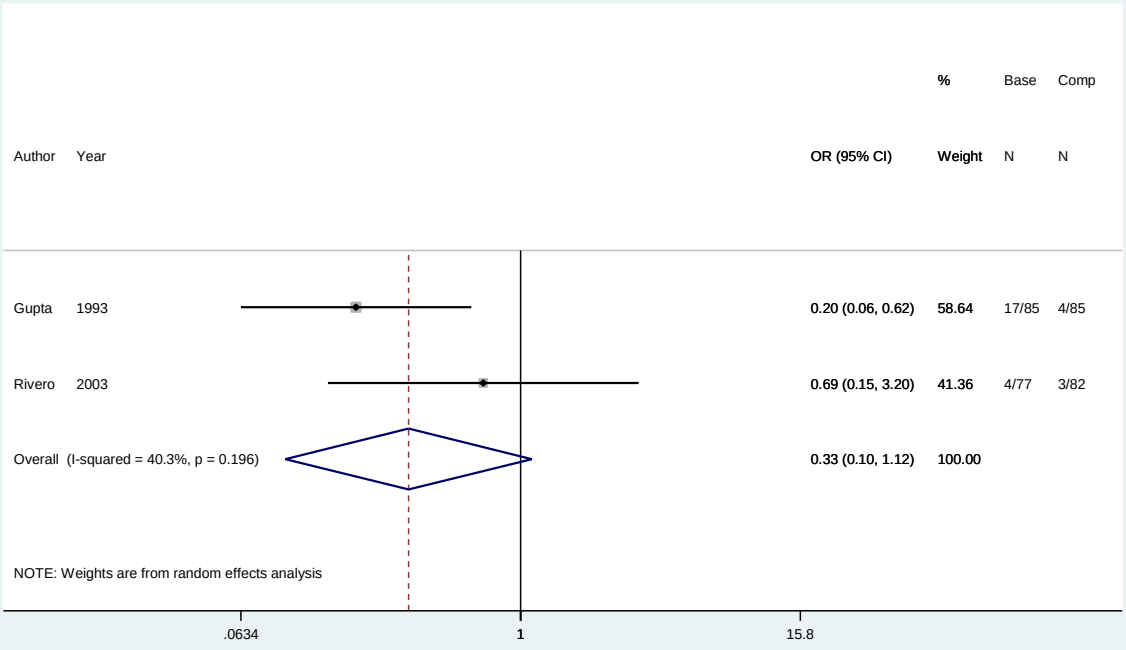




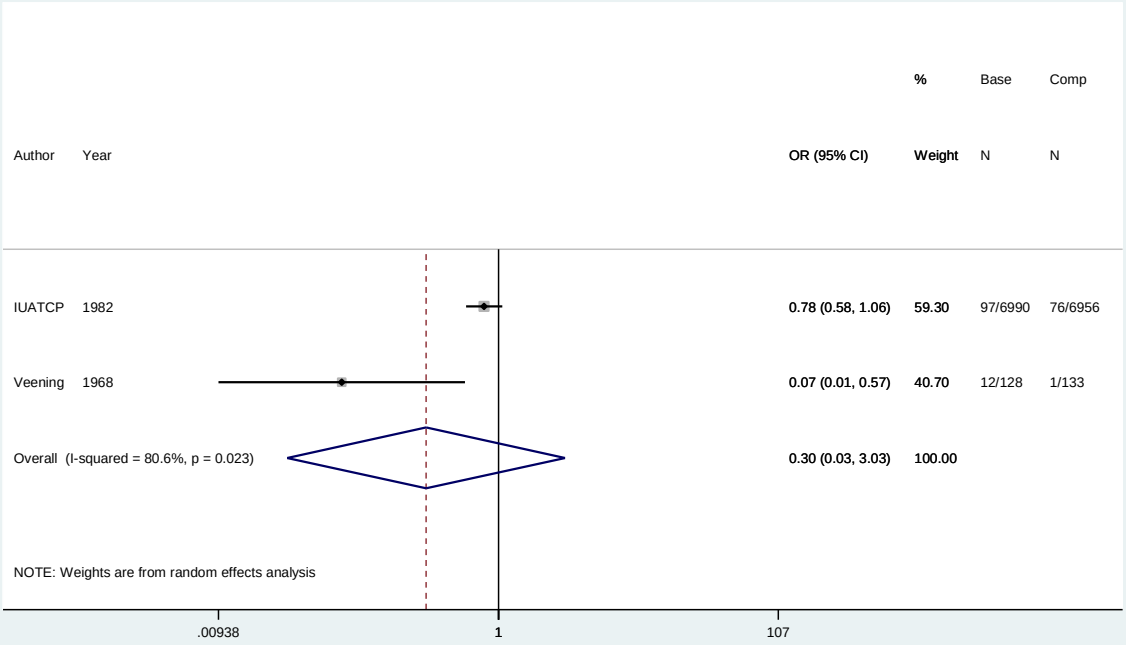
INH 12m vs. No treatment



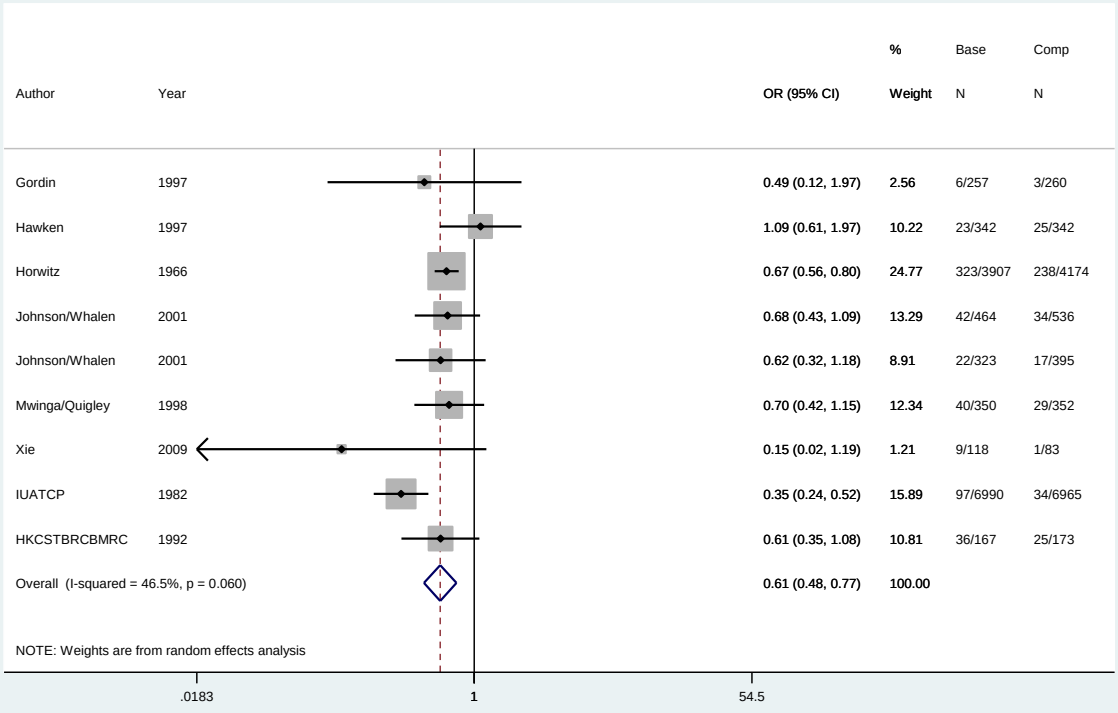
RMP-INH 3-4m vs. No treatment



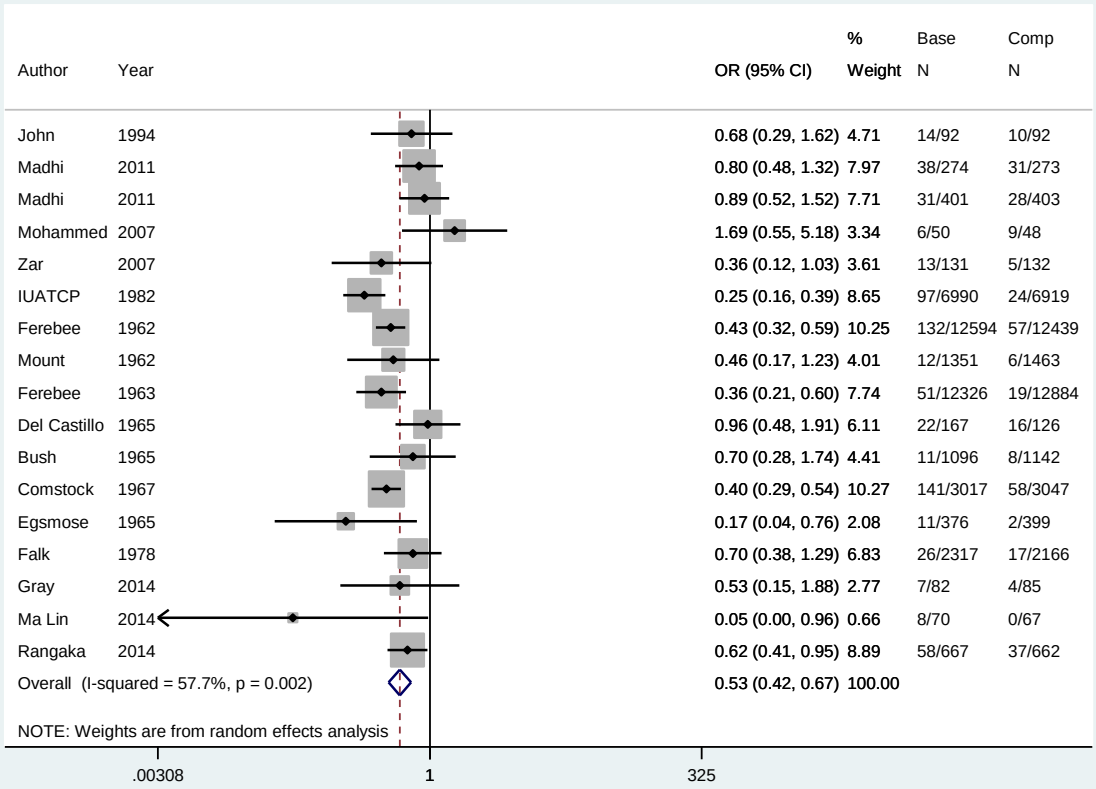
INH 3-4m vs. Placebo



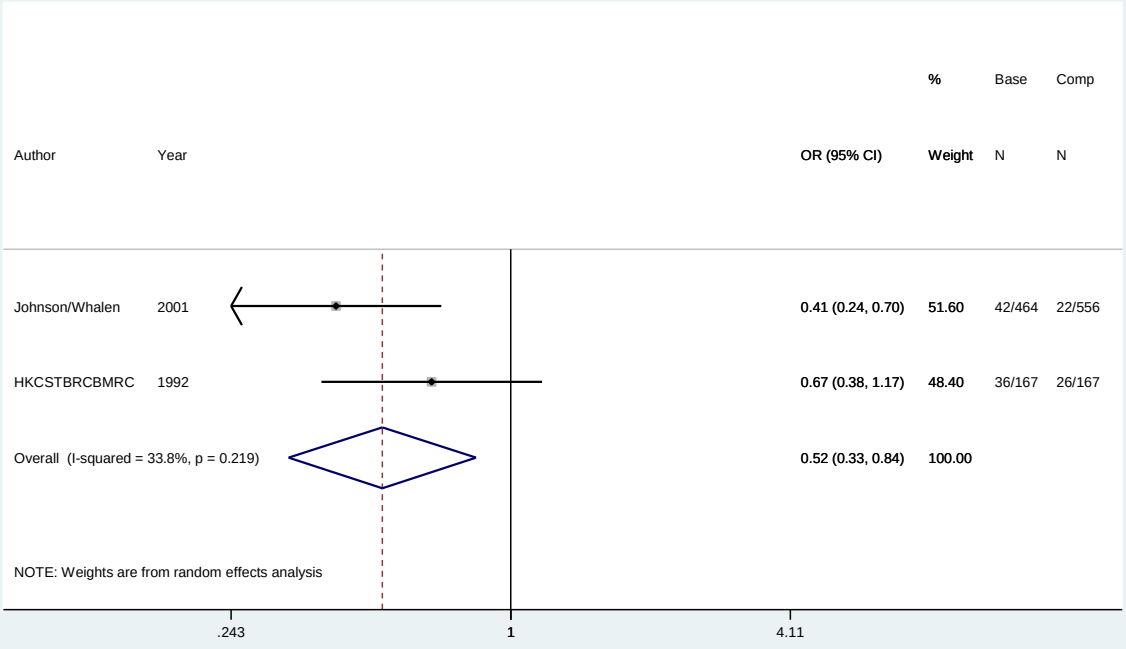
INH 6m vs. Placebo



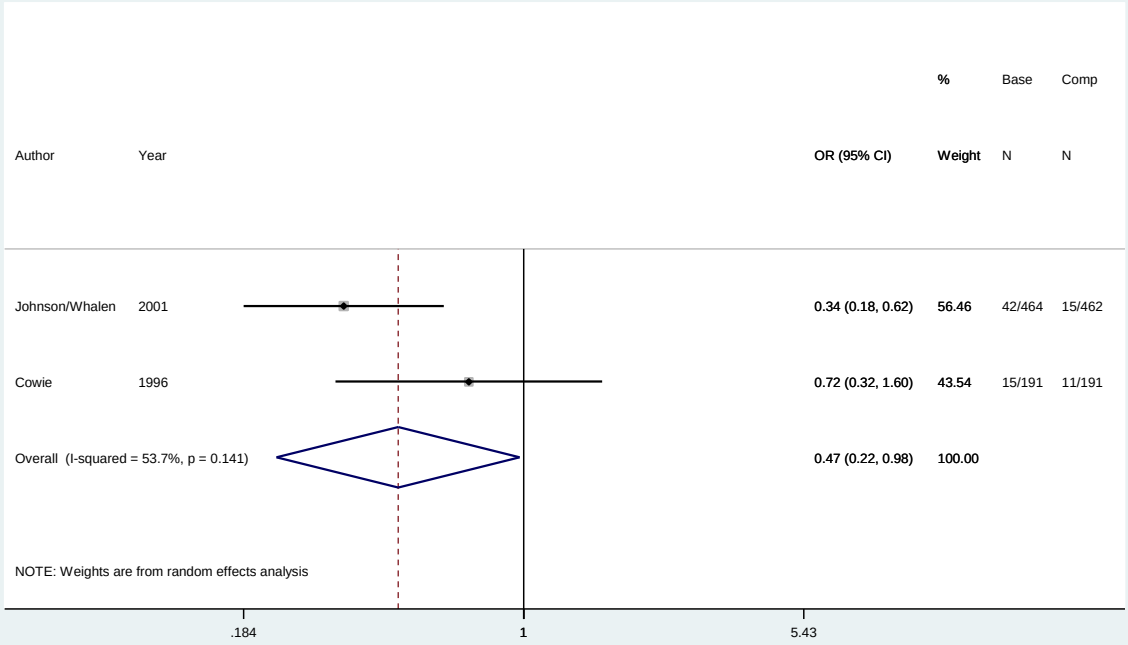
INH 12m vs. Placebo



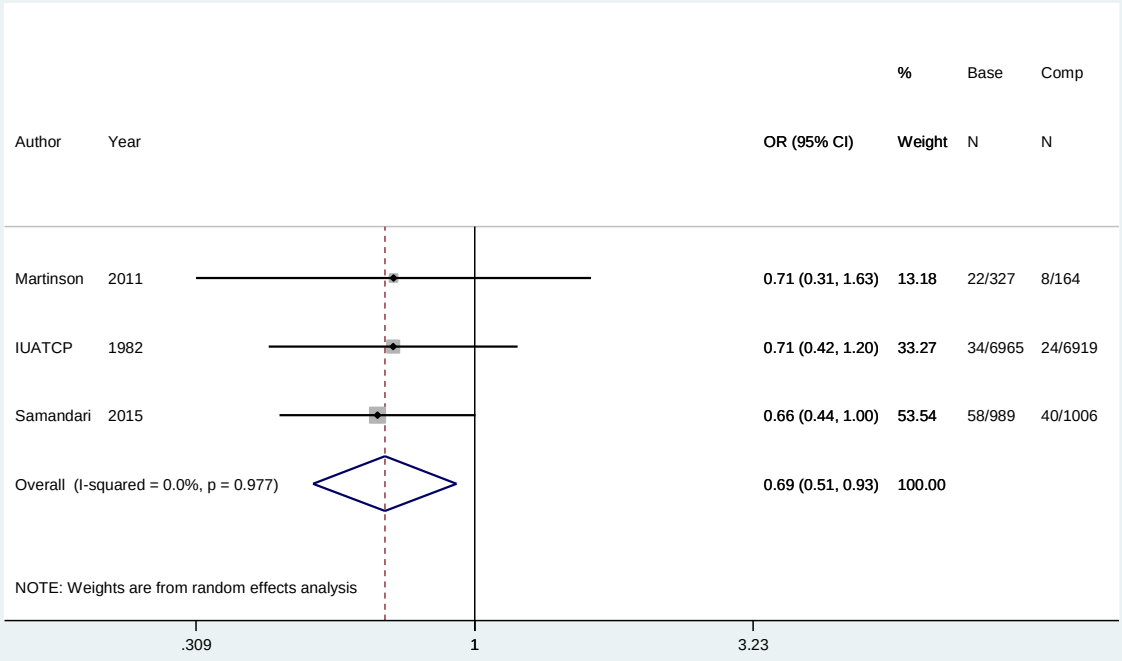
RMP-INH 3-4m vs. Placebo



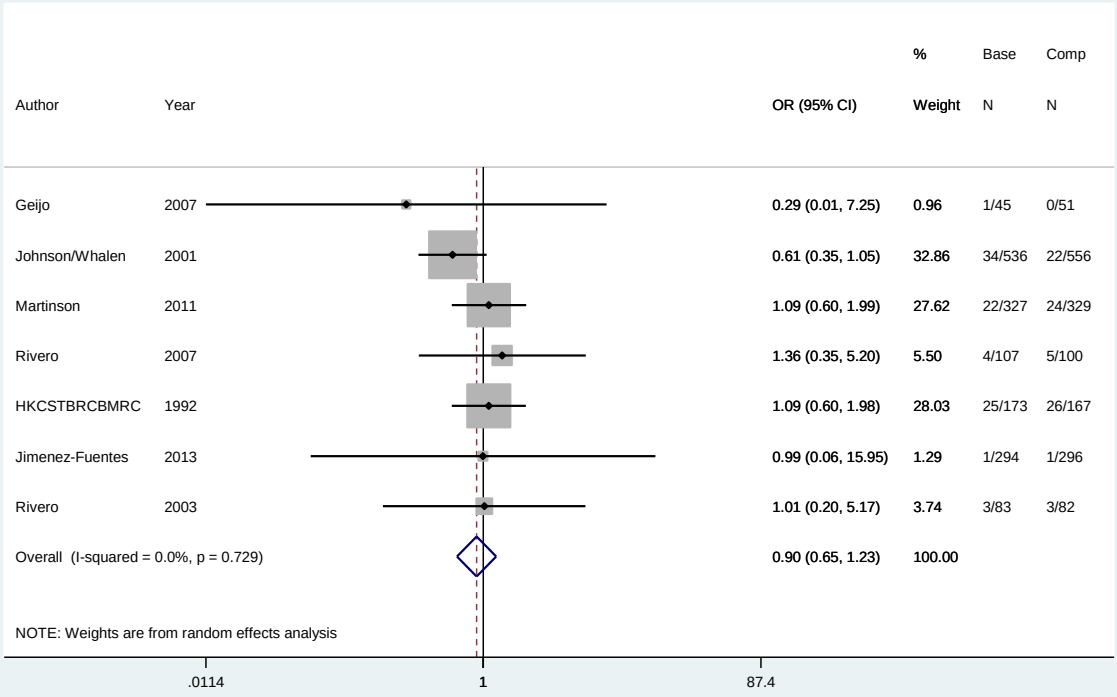
RMP-INH-PZA vs. Placebo



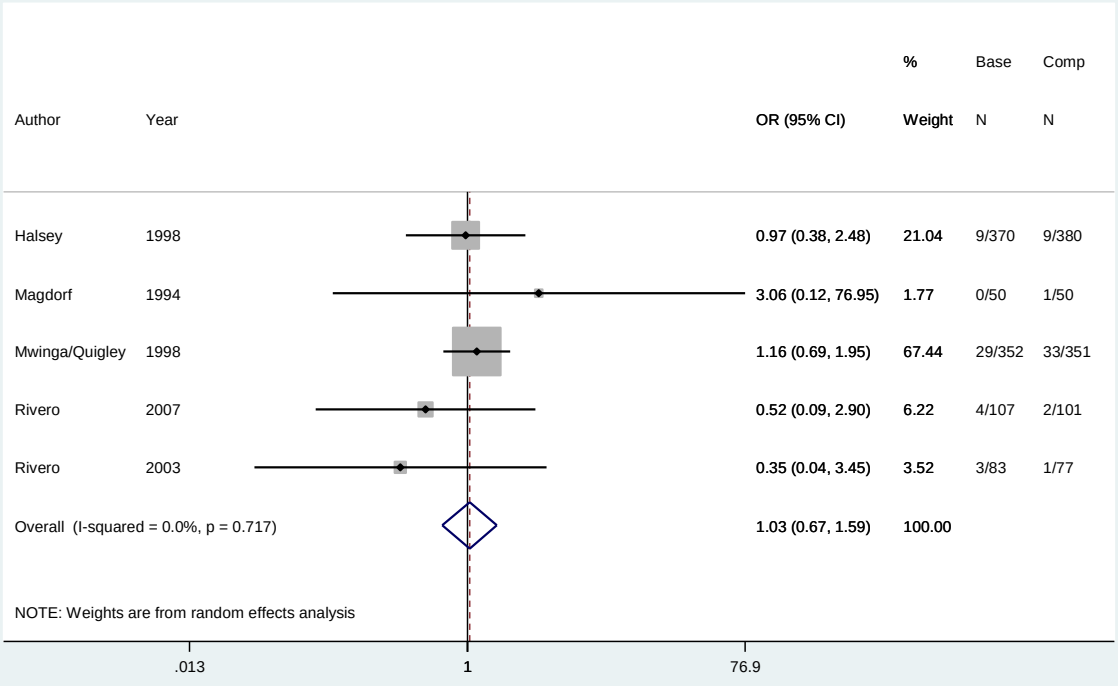
INH 12m vs. INH 6m



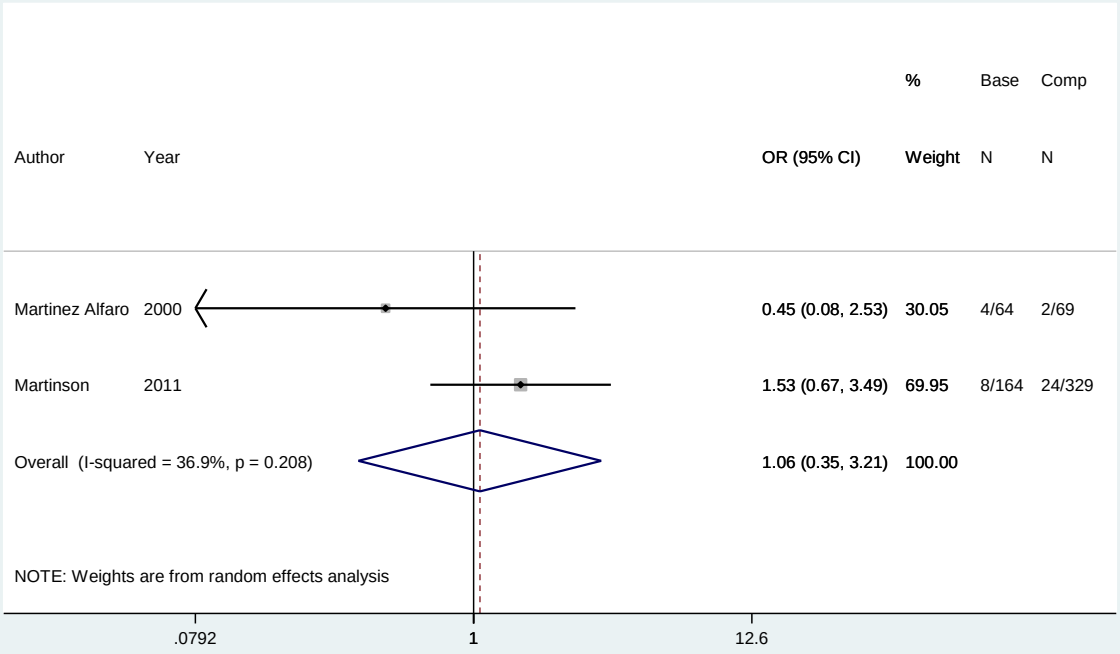
RMP-INH 3-4m vs. INH 6m



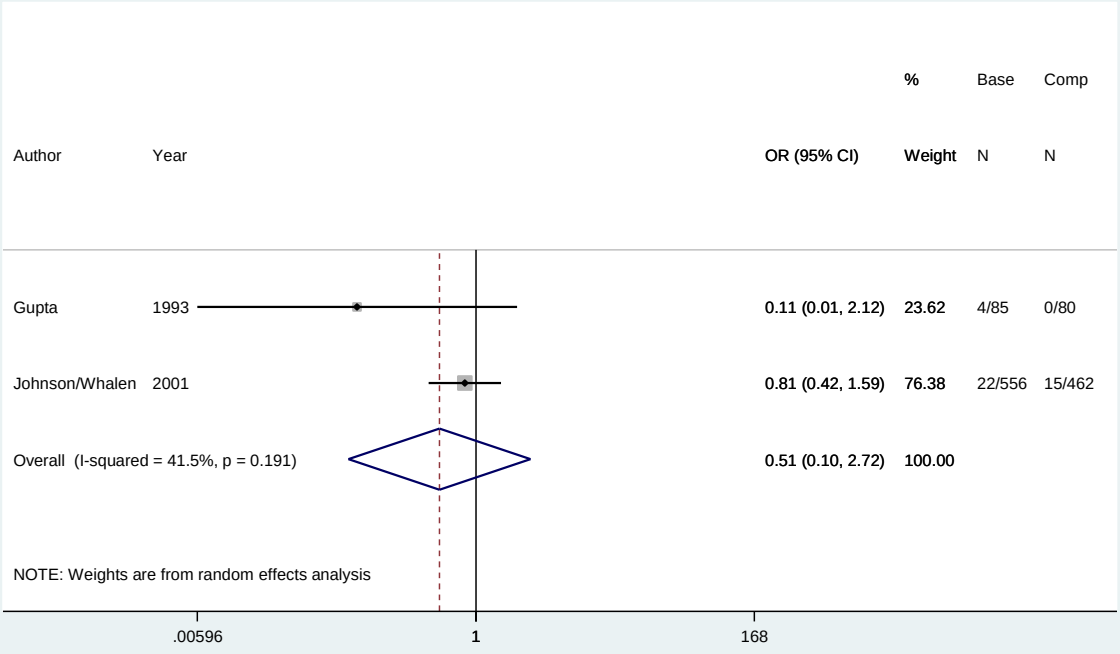
RMP-PZA vs. INH 6m

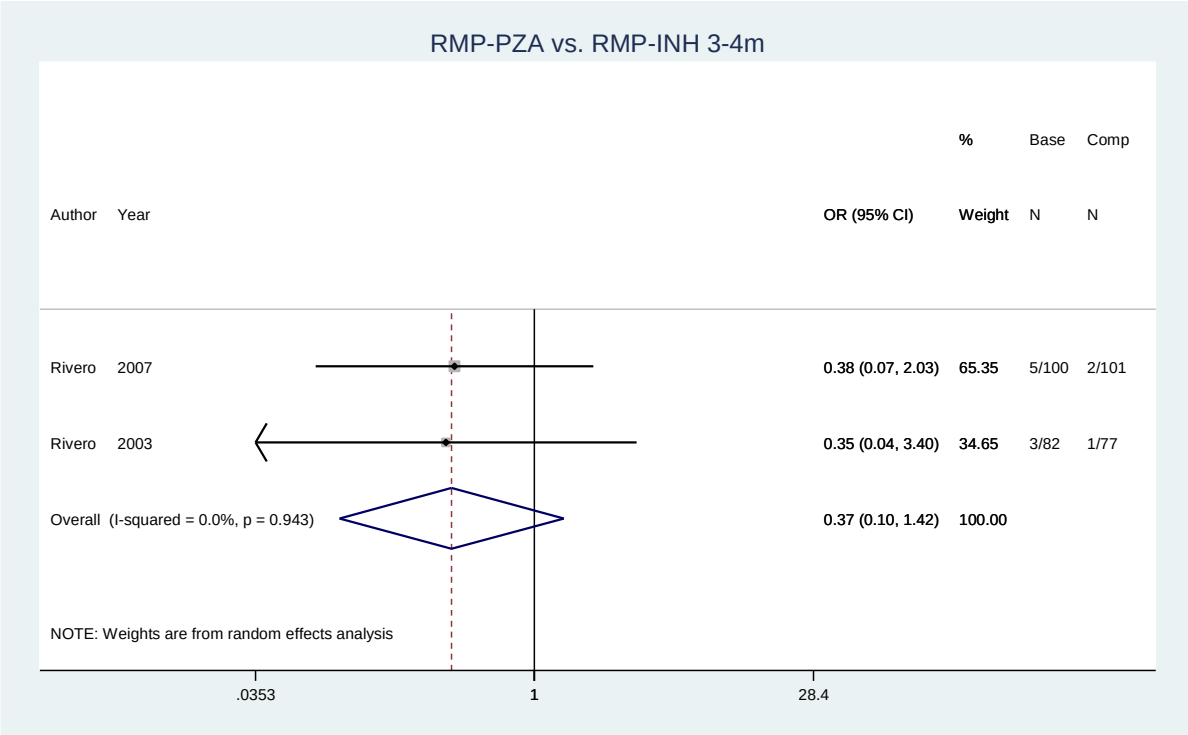


RMP-INH 3-4m vs. INH 12m

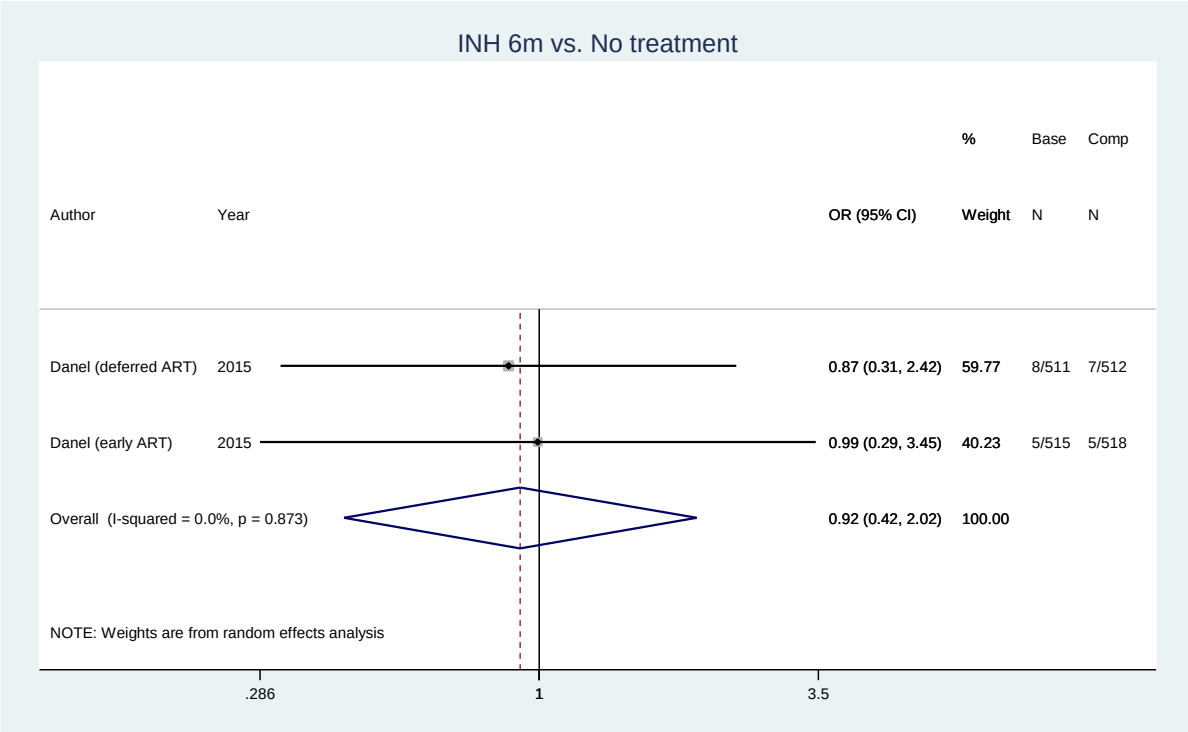


RMP-INH-PZA vs. RMP-INH 3-4m

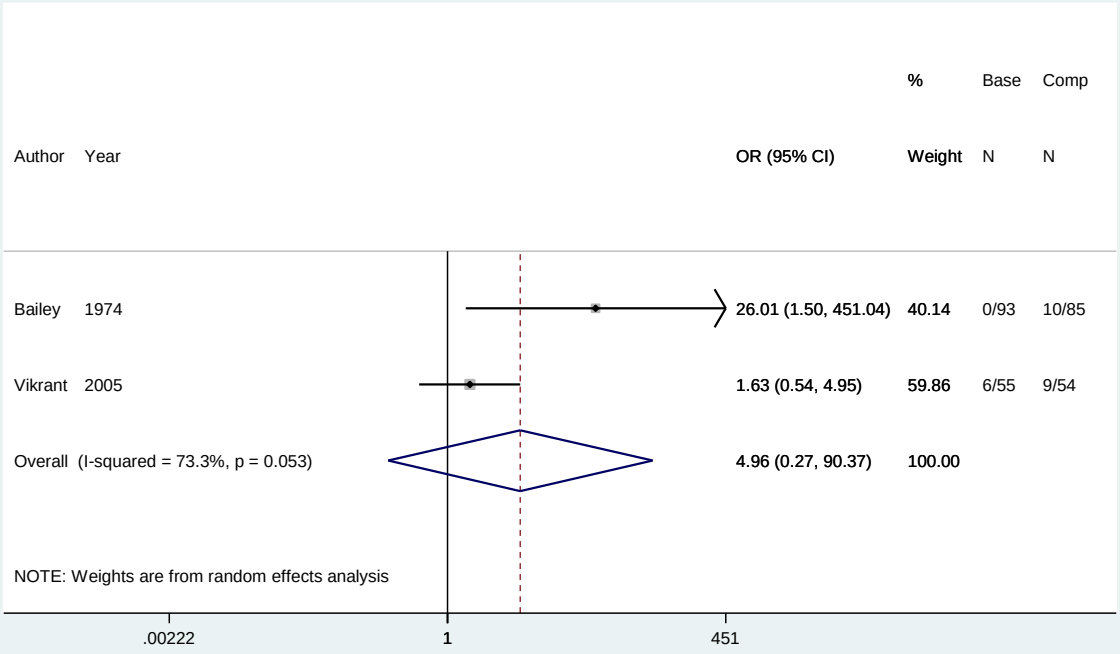



RMP-PZA vs. RMP-INH 3-4m
Author
Year
OR (95% CI)
% Weight
Base N
Comp N
Rivero 2007
0.38 (0.07, 2.03)
65.35
5/100
2/101
Rivero 2003
0.35 (0.04, 3.40)
34.65
3/82
1/77
Overall (I-squared = 0.0%, p = 0.943)
0.37 (0.10, 1.42)
100.00
NOTE: Weights are from random effects analysis
.0353
1
28.4

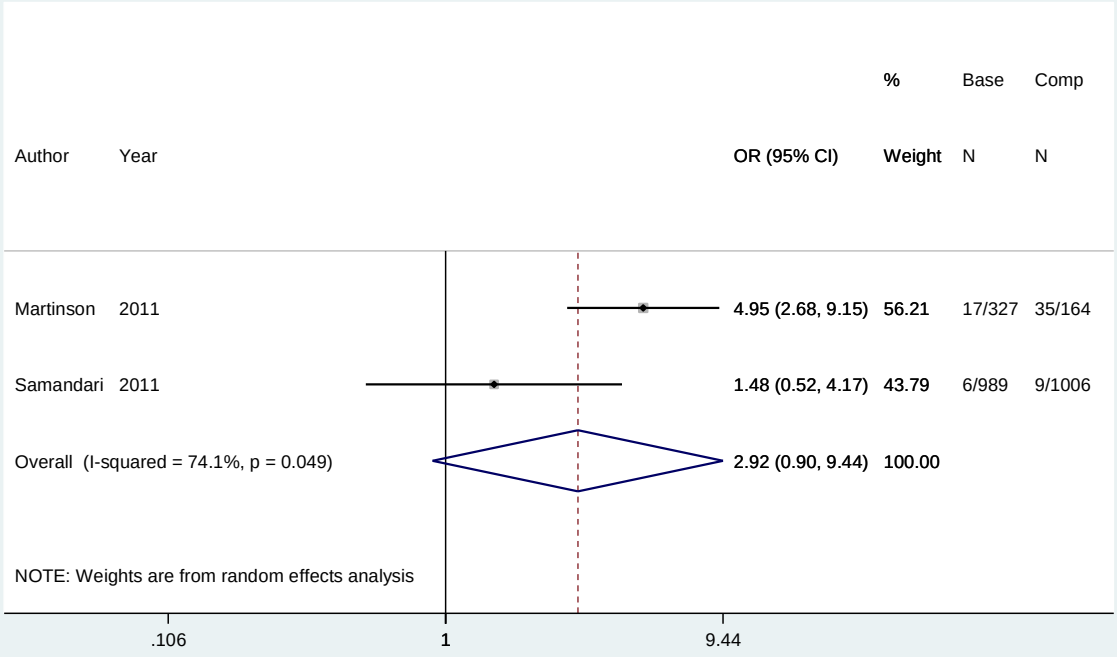
(b)


INH 6m vs. No treatment
Author
Year
OR (95% CI)
% Weight
Base N
Comp N
Danel (deferred ART) 2015
0.87 (0.31, 2.42)
59.77
8/511
7/512
Danel (early ART) 2015
0.99 (0.29, 3.45)
40.23
5/515
5/518
Overall (I-squared = 0.0%, p = 0.873)
0.92 (0.42, 2.02)
100.00
NOTE: Weights are from random effects analysis
.286
1
3.5

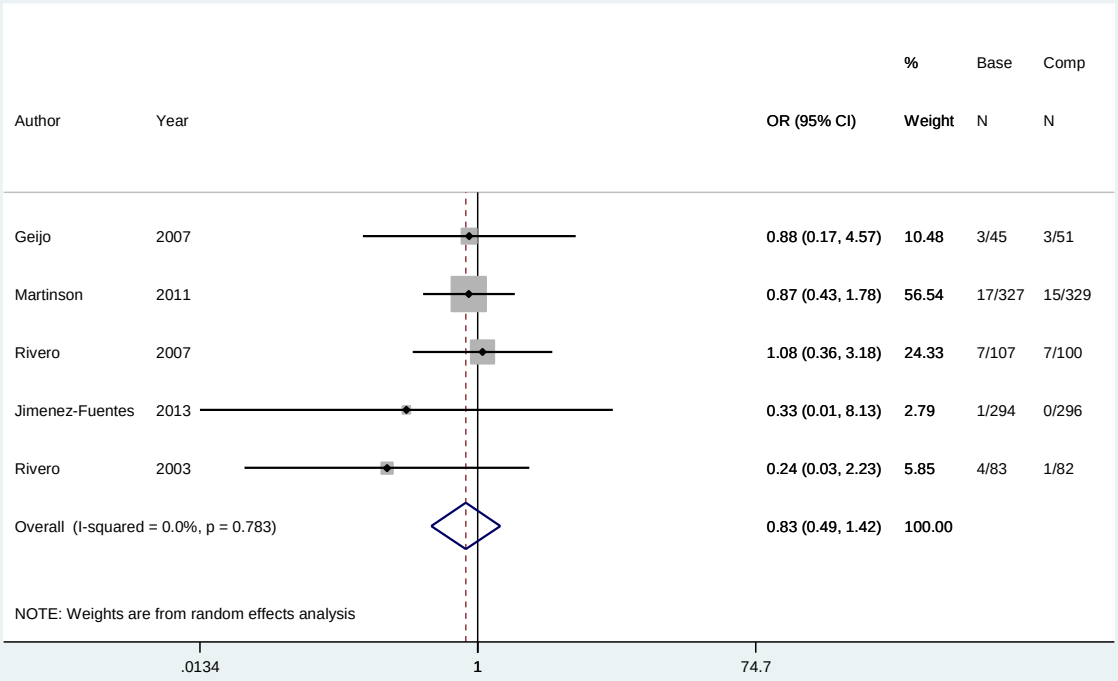
INH 12m vs. No treatment



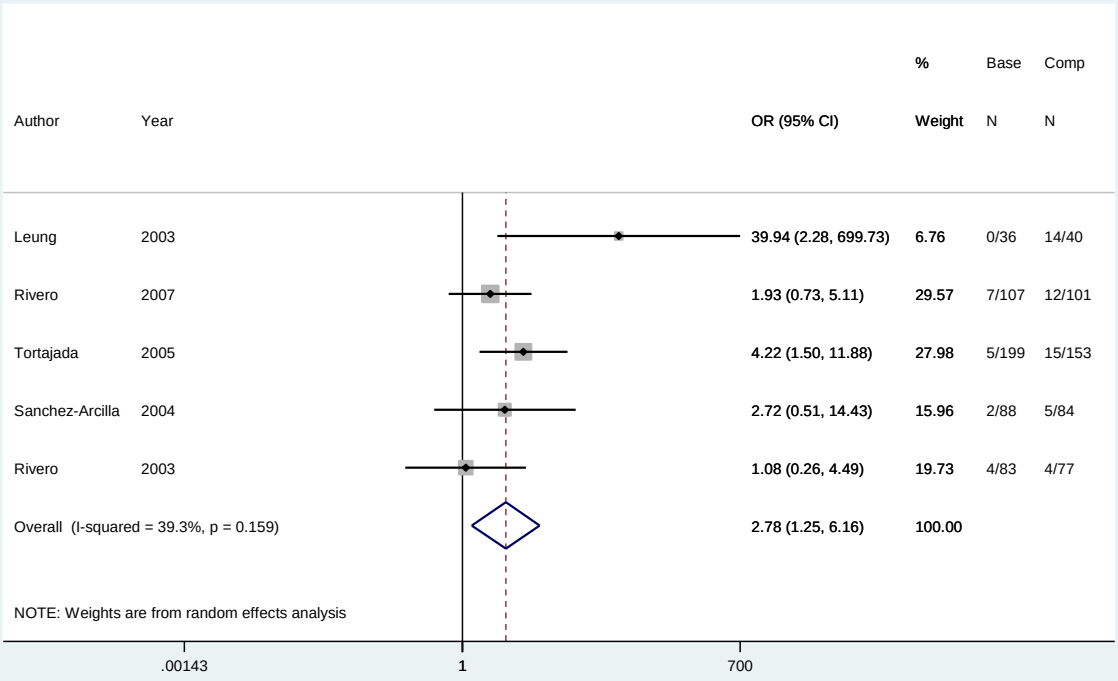
INH 12m vs. INH 6m



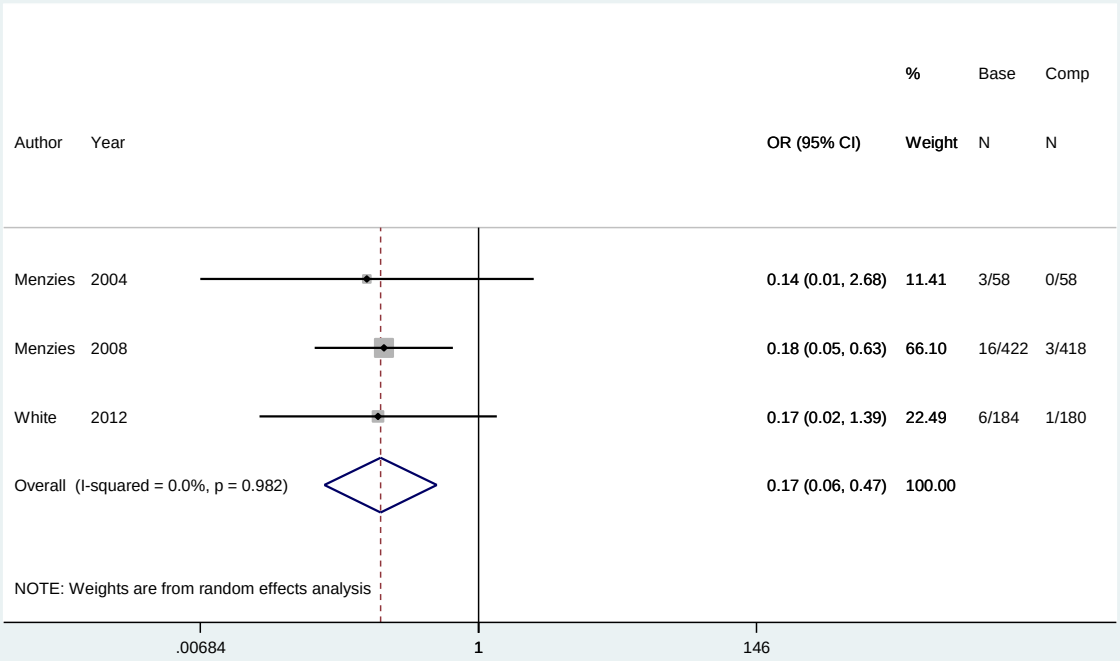
RMP-INH 3-4m vs. INH 6m



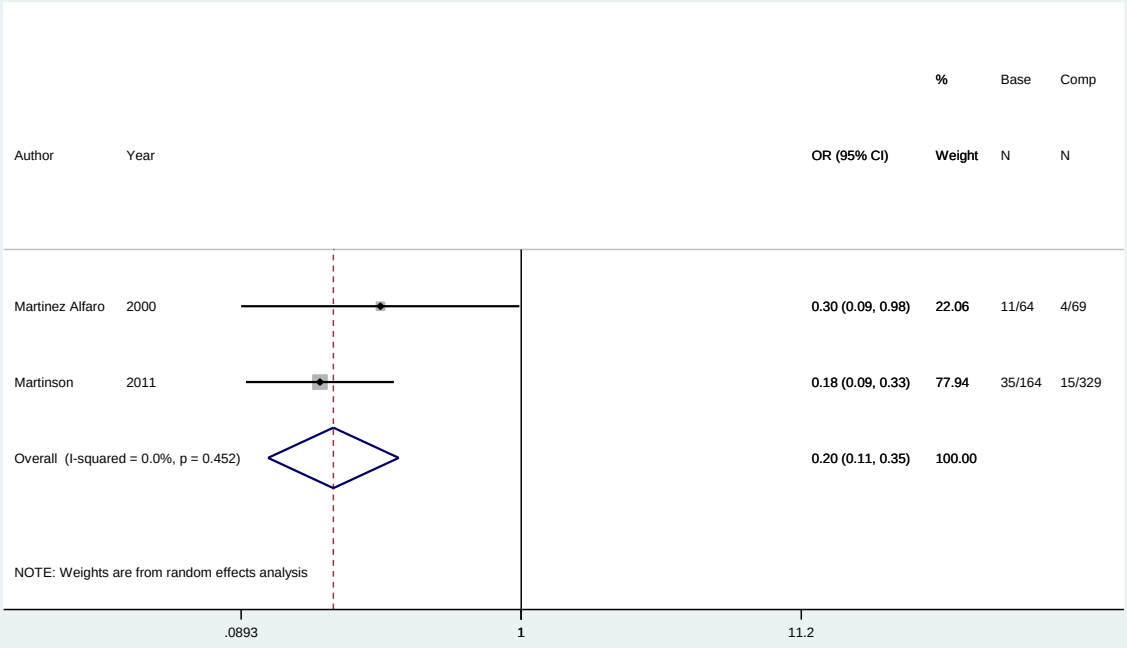
RMP-PZA vs. INH 6m

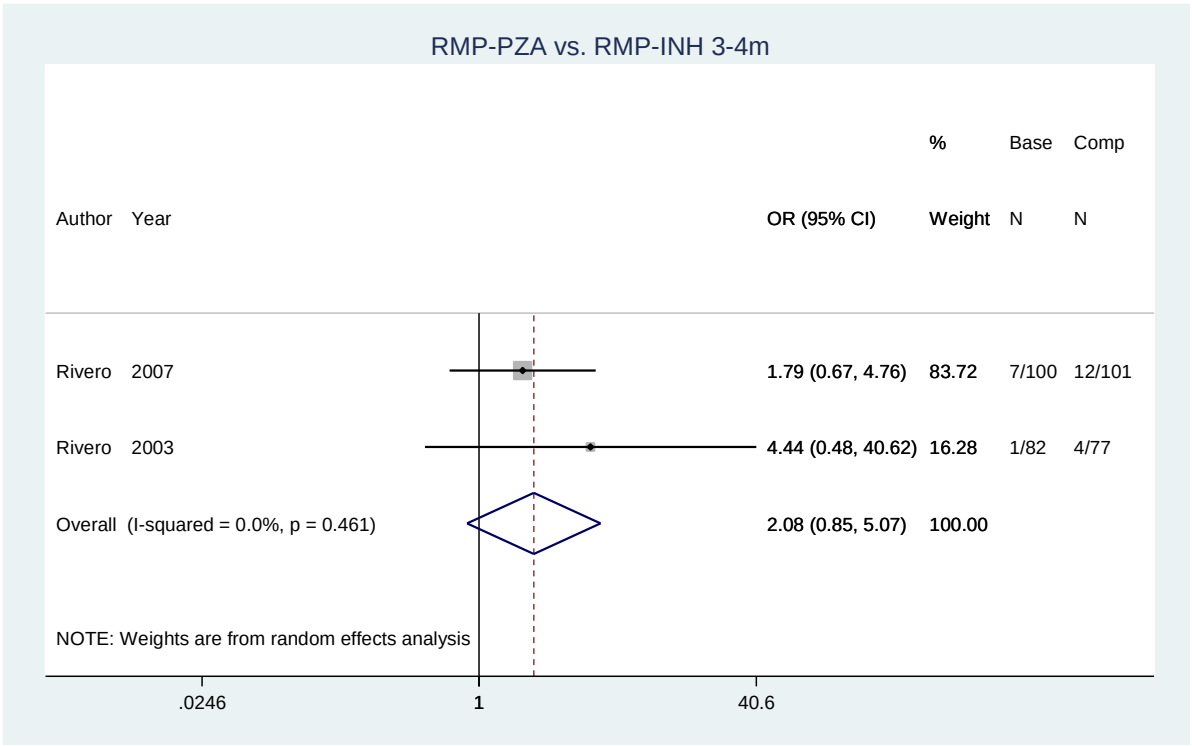


RMP vs. INH 9m



RMP-INH 3-4m vs. INH 12m



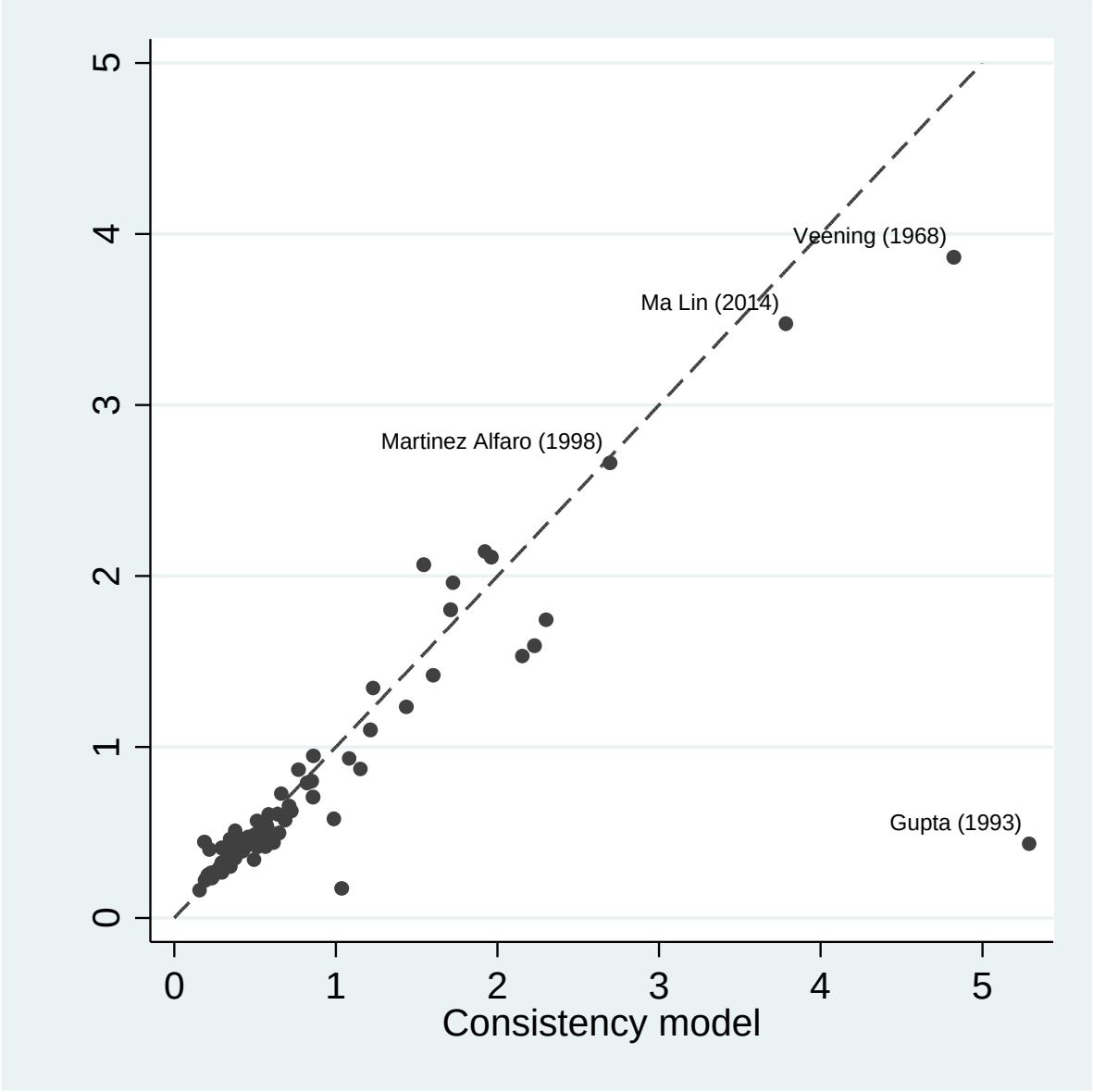

RMP-PZA vs. RMP-INH 3-4m
Author
Year
OR (95% CI)
% Weight
Base N
Comp N
Rivero 2007
1.79 (0.67, 4.76)
83.72
7/100
12/101
Rivero 2003
4.44 (0.48, 40.62)
16.28
1/82
4/77
Overall (I-squared = 0.0%, p = 0.461)
2.08 (0.85, 5.07)
100.00
NOTE: Weights are from random effects analysis
.0246
1
40.6

Data Supplement Material 11: Odds ratios for hepatotoxicity, derived from the network meta-analysis*

Regimen	OR vs. no treatment (95% CrI)	OR vs. placebo (95% CrI)	Rank (95% CrI)
No treatment	1.00 (1.00, 1.00)	0.24 (0.06, 0.75)	4 (2-7)
Placebo	4.12 (1.33, 15.88)	1.00 (1.00, 1.00)	9 (7-10)
INH 6m	1.10 (0.40, 3.17)	0.27 (0.10, 0.60)	5 (3-7)
INH 9m	1.70 (0.35, 8.05)	0.41 (0.08, 1.62)	6 (3-10)
INH 12m	2.72 (0.96, 7.44)	0.66 (0.26, 1.32)	8 (6-10)
RPT-INH	0.52 (0.13, 2.15)	0.13 (0.03, 0.42)	2 (1-5)
RMP	0.14 (0.02, 0.81)	0.03 (<0.02, 0.16)	1 (1-2)
RMP-INH 3-4m	0.72 (0.21, 2.37)	0.17 (0.05, 0.46)	3 (2-6)
RMP-INH-PZA	2.41 (0.25, 20.02)	0.58 (0.07, 3.72)	7 (2-10)
RMP-PZA	3.32 (0.99, 11.23)	0.80 (0.25, 2.17)	9 (6-10)

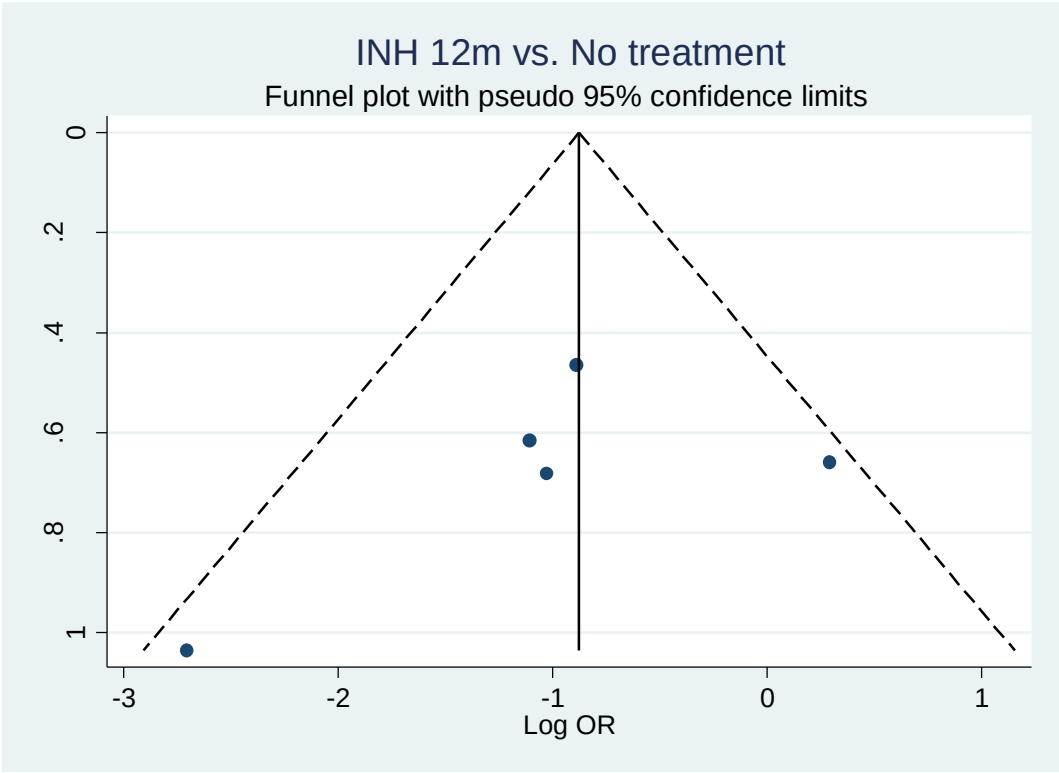
* Placebo ranked poorly for hepatotoxicity, which seems highly unusual (pooled random effects meta-analysis for placebo versus any INH regimen, 1.23 [0.73-2.07]). The evidence for this result is not based on a single, unusual, result it was reported from several trials. Gordin *et al.* 1997 reported 11 hepatotoxic events in each arm for placebo versus six months of INH in an HIV positive adult population from the Americas (OR 1.01 [95% CI 0.43-2.38]); John *et al.* 33 and 32 events (for a total of only 184 participants) for placebo versus 12 months of INH in Indian haemodialysis patients (0.95 [0.52-1.75]); Madhi *et al.* (HIV positive infants in sub-Saharan Africa) five events for placebo versus one for 12 months of INH (5.06 [0.59-43.56]); and Madhi *et al.* (HIV negative infants, same as previous) eight events for placebo versus three for 12 months of INH (2.71 [0.71-10.31]). The trials of Horwitz *et al.* and Mohammed *et al.* provide little or no information, with zero counts in all arms. Due to this the poor ranking of placebo, possibly a consequence of the patients who were studied developing symptoms and signs resulting from their co-morbid conditions such as chronic kidney disease or HIV infection, ORs with no treatment as a baseline are also presented here. CrI- credible interval, EMB- ethambutol, INH- isoniazid, m-months, OR- odds ratio, PZA- pyrazinamide, RFB- rifabutin, RMP- rifampicin, RPT- rifapentine

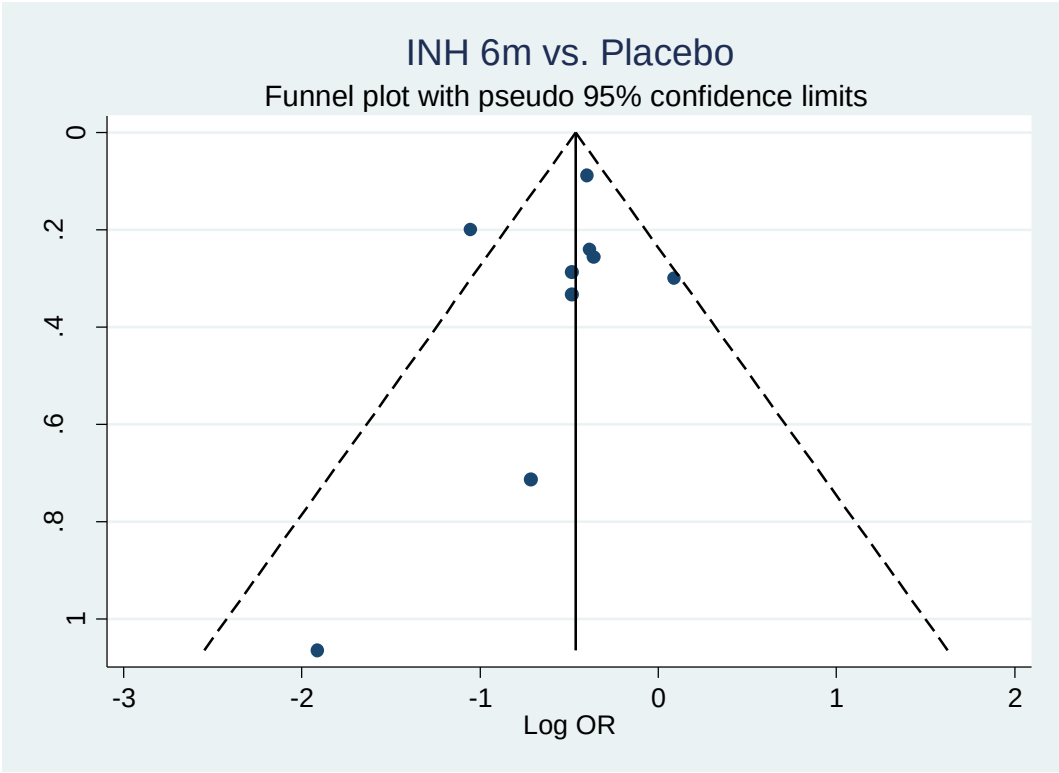
Data Supplement Material 12: Inconsistency plot for prevention of active tuberculosis*

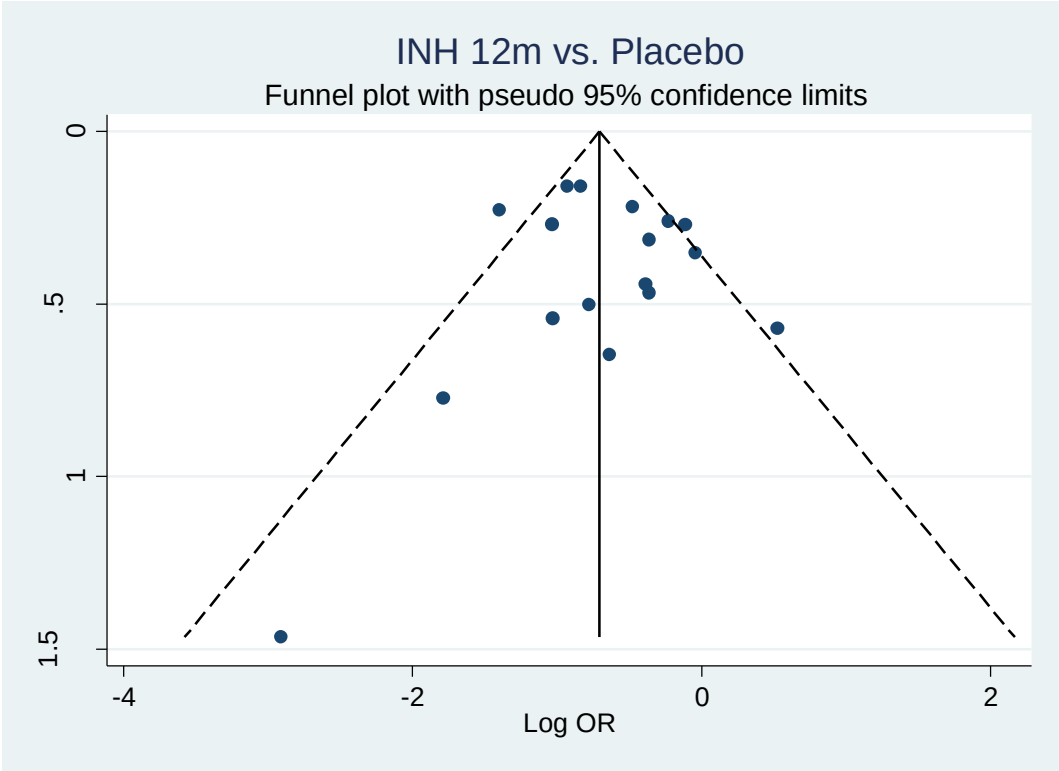


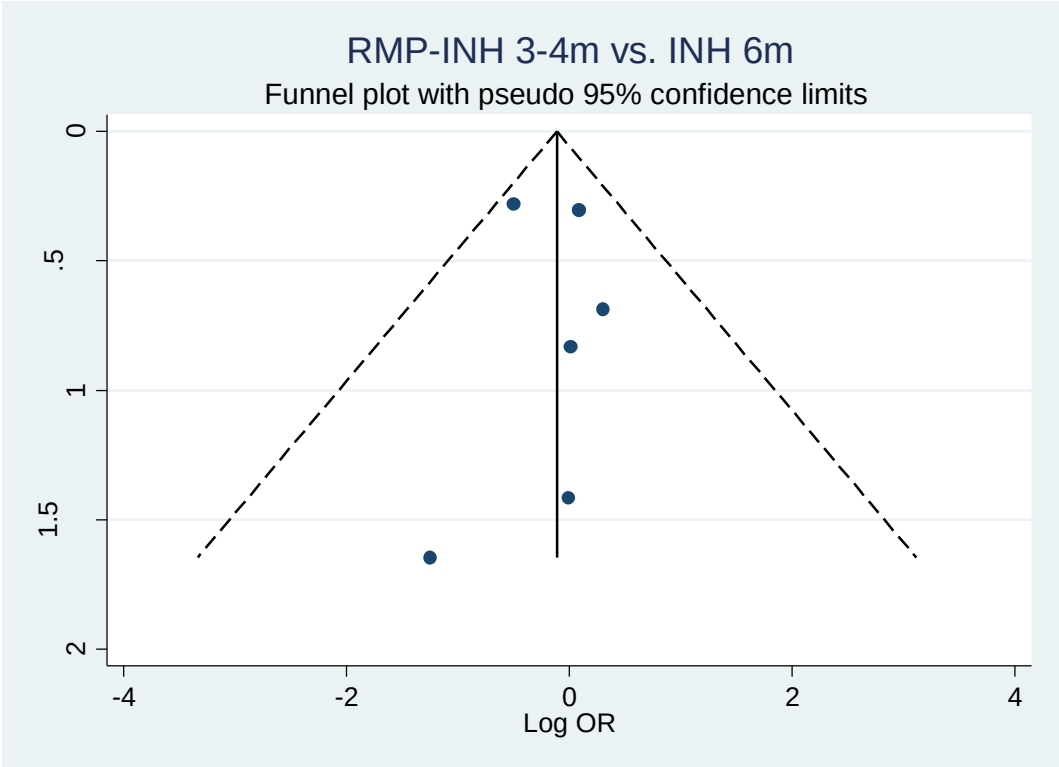
***** Inconsistency plot, showing study deviance, comparing that from the inconsistency model with that from the consistency model. Veening *et al* .study arm INH 4 months, Martinez Alfaro *et al.* study arm INH 9 months, Gupta *et al.* study arm, Ma Lin *et al*. study arm INH 12 months. RMP-INH-PZA. INH- isoniazid, PZA- pyrazinamide, RMP-rifampicin

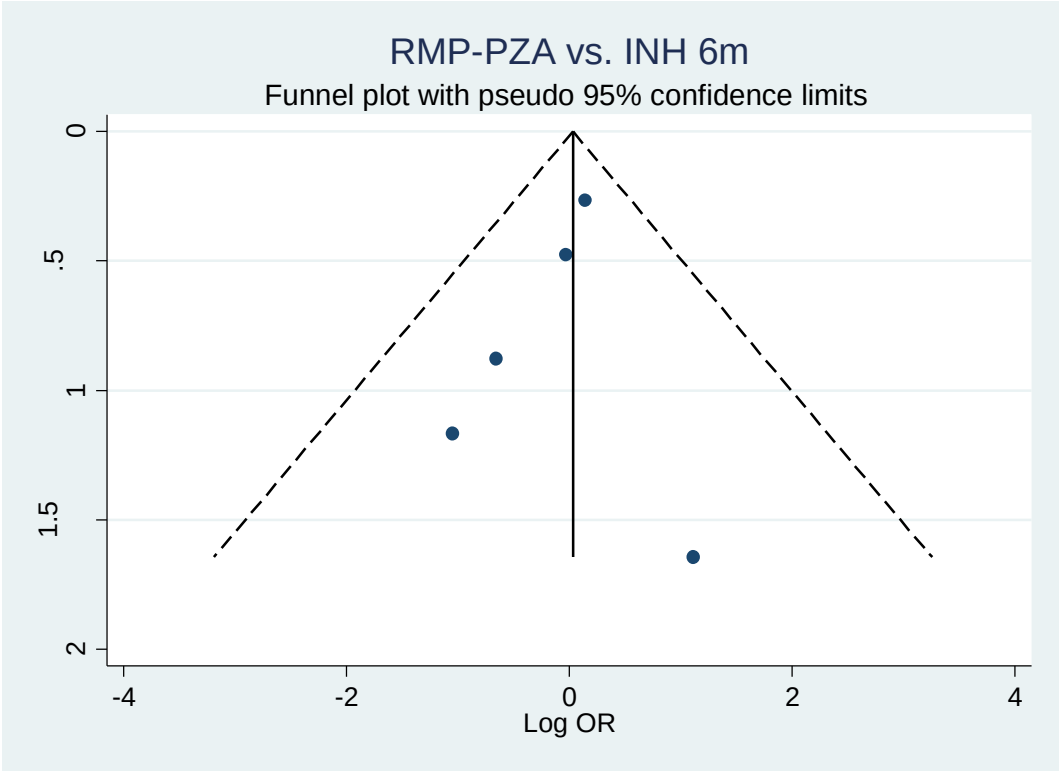
Data Supplement Material 13: Funnel plots for publication bias*






INH 12m vs. Placebo
Funnel plot with pseudo 95% confidence limits
0
.5
1
1.5
-4
-2
0
2
Log OR


RMP-INH 3-4m vs. INH 6m
Funnel plot with pseudo 95% confidence limits
0
.5
1
1.5
2
-4
-2
0
2
4
Log OR



* Funnel plots to assess publication bias where N>4 (Tables 2 and 3) for a) no treatment vs. INH 12-72 months, b) placebo vs. INH 6 months, c) placebo vs. INH 12-72 months, d) INH 6 months vs. RMP-INH 3-4 months. All active tuberculosis outcome. INH- isoniazid, OR- odds ratio, RMP- rifampicin, SE- standard error

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